

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
15 February 2001 (15.02.2001)

PCT

(10) International Publication Number
WO 01/10842 A2

(51) International Patent Classification⁷: C07D 239/00

Cambridge, MA 02141 (US). DAI, Mingshi [CN/US]; 7 Avondale Avenue, Billerica, MA 01821 (US). VOS, Tricia, J. [US/US]; One Willow Street, Apt. #2, Belmont, MA 02478 (US).

(21) International Application Number: PCT/US00/21327

(74) Agents: HANLEY, Elizabeth, A.; Lahive & Cockfield, LLP, 28 State Street, Boston, MA 02109 et al. (US).

(22) International Filing Date: 4 August 2000 (04.08.2000)
(25) Filing Language: English

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(26) Publication Language: English
(30) Priority Data:
60/147,288 4 August 1999 (04.08.1999) US
60/223,277 3 August 2000 (03.08.2000) US

(71) Applicant (*for all designated States except US*): MILLENNIUM PHARMACEUTICALS, INC. [US/US]; 75 Sidney Street, Cambridge, MA 02139 (US).
(72) Inventors; and
(75) Inventors/Applicants (*for US only*): MAGUIRE, Martin, P. [US/US]; 169 Msgr. O'Brien Hwy. Apt. #507,

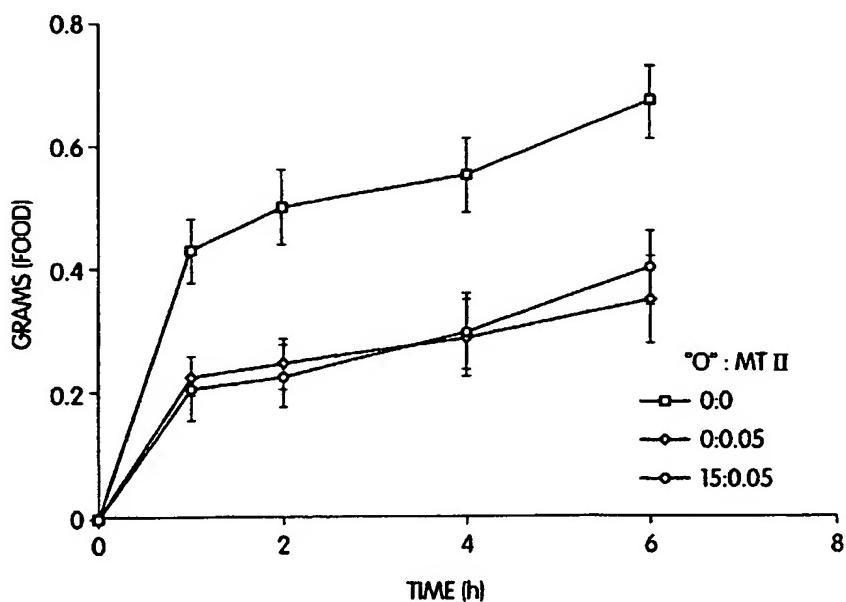
(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: MELANOCORTIN-4 RECEPTOR BINDING COMPOUNDS AND METHODS OF USE THEREOF



WO 01/10842 A2



(57) Abstract: MC4-R binding compounds of the formula (I): B-Z-E wherein B is an anchor moiety, Z is a central moiety, and E is an MC4-R interacting moiety are discussed. Methods of using the compounds to treat MC4-R associated disorders, such as disorders associated with weight loss, are also discussed.



Published:

- *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

**MELANOCORTIN-4 RECEPTOR BINDING COMPOUNDS AND METHODS
OF USE THEREOF**

5 **Background**

Melanocortins are known to have a broad array of physiological actions (Nakanishi, et al. *Nature* (1979) 278:423-427). Aside from their well known effects on adrenal cortical functions and on melanocytes, melanocortins have been shown to affect behavior, learning, memory, control of the cardiovascular system, analgesia, 10 thermoregulation, and the release of other neurohumoral agents including prolactin, luetinizing hormone, and biogenic amines (De Weid et al. *Methods Achiev. Exp. Pathol.* (1991) 15:167-199; De Weid et al. *Physiol. Rev.* (1982) 62:977-1059; Gruber, K.A. et al. *Am. J. Physiol.* (1989) 257:R681-R694; Murphy et al. *Science* (1980) 210:1247-1249; Murphy et al. *Science* (1983) 221:192-193; Ellerkmann, E. et al. *Endocrinol.* 15 (1992) 130:133-138; Versteeg, D.H.G. et al. *Life Sci.* (1986) 38:835-840). Peripherally, melanocortins have been identified to have immunomodulatory and neurotrophic properties, and to be involved in events surrounding partition (Cannon, J.G. et al. *J. Immunol.* (1986) 137:2232-2236; Gispen, W.H. *Trends Pharm. Sci.* (1992) 11:221-222; Wilson, J.F. *Clin. Endocrinol.* (1982) 77:233-242; Clark, D. et al. *Nature* (1978) 273:163-164; Silman, R.E. et al. *Nature* (1976) 260:716-718). Furthermore, 20 melanocortins are present in a myriad of normal human tissues including the brain, ovary, lung, thyroid, liver, colon, small intestine and pancreas (Tatro, J.B. et al. *Endocrinol.* (1987) 121:1900-1907; Mountjoy, K.G. et al. *Science* (1992) 257:1248-1251; Chhajlani, V. et al., *FEBS Lett.* (1992) 309:417-420; Gantz, L. et al., *J. Biol. Chem.* (1993) 268:8246-8250; Gantz, L. et al., *J. Biol. Chem.* (1993) 268:15174-15179).

Recent studies have described an unexpected diversity of subtypes of receptors for the melanocortin peptides and determined that they belong to the superfamily of seven transmembrane G-protein linked cell surface receptors (Mountjoy, K.G. et al., *Science* (1992), *supra*; Chhajlani, V. et al., *FEBS Lett.* (1992), *supra*). Five melanocortin 30 receptor subtypes have been cloned. The melanocortin-1 (MC1) receptor is found in melanoma cells, where it has a role in mediating pigmentation. The melanocortin-2 receptor (MC2-R or ACTH receptor) is found in the adrenal glands where it mediates

-2-

the effects of ACTH (adrenocorticotropic hormone). The melanocortin-3 receptor (MC3-R) is primarily found in the central nervous system (CNS) (Gantz, L. et al., *J. Biol. Chem.* (1993) 268:8246-8250), but its physiological function is still unknown. The melanocortin-4 receptor (MC4-R) has been found in the brain, where it is widely distributed in several areas, including the cortex, thalamus, hypothalamus, brain stem, and spinal cord (Gantz, L. et al. *J. Biol. Chem.* (1993) 268:15174-15179; Mountjoy, K.G. et al. *Mol. Endocrinol.* (1994) 8:1298-1308). MC4-R has recently been related to weight homeostasis. MC4-R "knock out" mice have been shown to develop obesity (Huszar et al. *Cell* (1997) 88:131-141). The feeding behavior leading to the obesity can be inhibited by injection of MSH peptides (Vergoni et al. *Neuropeptides* (1986) 7:153-158; Vergoni et al. *Eur. J. Pharmacol.* (1990) 179:347-355; Fan et al. *Nature* (1997) 385:165-168). The melanocortin-5 receptor (MC5-R) has a wide peripheral distribution and is believed to participate in the regulation of the exocrine gland function (Chen et al. *Cell* (1997) 91:789-798).

15

Summary

In one aspect, the invention pertains to a method for treating a melanocortin-4 receptor (MC4-R) associated state in a mammal. The method involves administering an effective amount of a MC4-R binding compound to a mammal, such that the MC4-R associated state is treated. The MC4-R binding compound is of the formula (I):



wherein B is an anchor moiety, Z is a central moiety, E is a MC4-R interacting moiety, and pharmaceutically acceptable salts, thereof.

In a further embodiment, the MC4-R binding compound is of the formula (II):



30 wherein B is an anchor moiety, A is cyclic moiety, E is a MC4-R interacting moiety, and pharmaceutically acceptable salts, thereof.

-3-

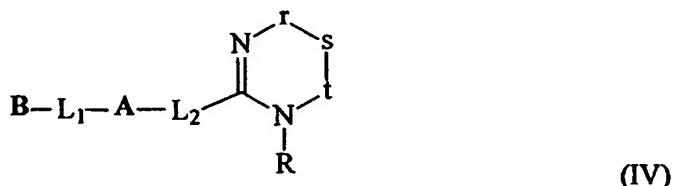
In another embodiment, the invention pertains to another method for treating an MC4-R associated state in a mammal, by administering to a mammal an effective amount of a MC4-R binding compound of formula (III):

5

B-L₁-A-L₂-E (III)

wherein B is an anchor moiety, L₁ and L₂ are linking moieties, A is a cyclic moiety, E is a MC4-R interacting moiety, and pharmaceutically acceptable salts thereof.

- The invention also pertains to treating MC4-R associated states with an MC4-R binding compound of formula III, wherein B is substituted or unsubstituted biaryl, unsubstituted or substituted heterocyclic, or unsubstituted or substituted phenyl, wherein one or more of said substituents are halogens, alkyl, alkynyl, alkoxy, aryl, amino, cyano, or nitro; L₁ is a covalent bond, C₁-C₁₀ branched or unbranched alkyl, wherein one or two of the carbons are optionally replaced with oxygen, sulfur or nitrogen atoms; L₂ is a covalent bond, substituted or unsubstituted amino, ether, thioether, or alkyl; E is substituted or unsubstituted alkyl, amino, amidino, guanidino, heterocyclic, or aryl, wherein said substituents are amino, arylalkyl, aminoalkyl, alkyl, aryl, alkenyl, or alkynyl; and A is a substituted or unsubstituted phenyl, heteroaryl, cycloalkyl, or biaryl, and pharmaceutically acceptable salts thereof.
- 10 In another embodiment, the invention pertains to a method for treating an MC4-R associated state in a mammal by administering an effective amount of a MC4-R binding compound to a mammal, such that the MC4-R associated state is treated. In this embodiment, the compound is of the formula (IV):



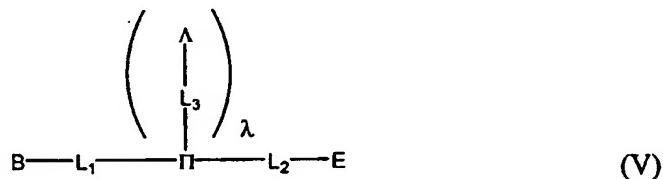
- 25 wherein B is substituted or unsubstituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl, or heteroaryl; A is aryl, heteroaryl, biaryl, cycloalkyl, heterocyclic, or cycloalkenyl; L₁ and L₂ are selected from the group consisting of a covalent bond, C₁-C₆ branched or unbranched alkyl, wherein one or two of the carbons are optionally replaced with oxygen, sulfur or nitrogen atoms; r is a covalent bond, CH, CH₂, CR¹, CR¹R², or H; t is

-4 -

CH, CH₂, CR³, CR³R⁴, or H; s is CHR₅, CR₅, CR₅R₆ or absent (e.g., leaving a non-cyclic diamine); R is H, substituted or unsubstituted alkyl, arylalkyl, or heteroalkyl, and may optionally be linked to A, B, L₁, or L₂; R¹, R², R³, R⁴, R⁵, and R⁶ are each substituted or unsubstituted alkyl, alkenyl, halogen, thiol, or alkoxy, and may optionally be linked to form a carbocyclic or heterocyclic ring. Pharmaceutically acceptable salts of the MC4-R binding compound are also included.

The invention also pertains to methods for treating an MC4-R associated state in a mammal by administering an effective amount of a MC4-R binding compound of the formula (V):

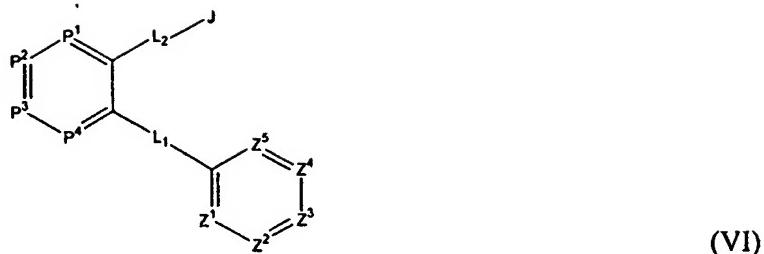
10



wherein B is substituted or unsubstituted biaryl, unsubstituted or substituted heterocyclic, or unsubstituted or substituted phenyl, wherein one or more of said substituents are halogens, alkyl, alkynyl, alkoxy, aryl, amino, cyano, or nitro; L₁ is a covalent bond, C₁-C₁₀ branched or unbranched alkyl, wherein one or two of the carbons are optionally replaced with oxygen, sulfur or nitrogen atoms; L₂ is a covalent bond, substituted or unsubstituted amino, ether, thioether, or alkyl; E is substituted or unsubstituted alkyl, amino, amidino, guanidino, heterocyclic, or aryl, wherein said substituents are amino, arylalkyl, aminoalkyl, alkyl, aryl, alkenyl, or alkynyl; Π is a covalent bond, a carbon atom, a nitrogen atom, heterocyclic, alkyl, cycloalkyl, or aryl; L₃ is a covalent bond, C₁-C₆ branched, unbranched or cyclic alkyl, wherein one, two or three of the carbons are optionally replaced with oxygen, sulfur or nitrogen atoms, carbonyl, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, or aminothiocarbonyl; and Λ is heterocyclic, aryl, alkoxy, amino, alkyl, alkenyl, alkynyl, or hydrogen; and λ is 0, 1 or 2, and pharmaceutically acceptable salts thereof.

In yet another embodiment, the invention also pertains to a method for treating an MC4-R associated state in a mammal by administering an effective amount of a MC4-R binding compound to a mammal, wherein the compound is an MC4-R antagonist, and is of the formula (VI):

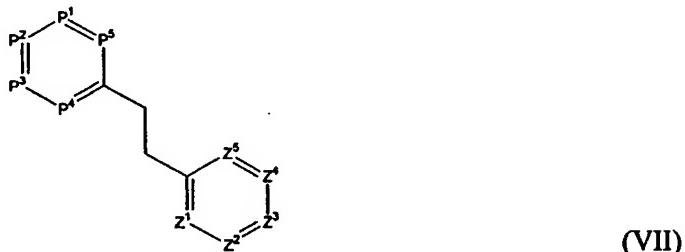
-5-



wherein

- P¹, P², P³, P⁴, and P⁵ are optionally substituted carbon, sulfur, or nitrogen, and
 5 wherein one of P¹, P², P³, P⁴ and P⁵ may represent a covalent bond; Z¹, Z², Z³, Z⁴, and Z⁵
 are optionally substituted carbon or nitrogen; L₁ is a covalent bond, C₁-C₁₀ branched or
 unbranched alkyl, wherein one or two of the carbons are optionally replaced with
 oxygen, sulfur or nitrogen atoms; L₂ is a covalent bond, substituted or unsubstituted
 amino, ether, thioether, or alkyl; and J is an unsubstituted or substituted nitrogen
 10 containing heterocycle or a substituted or unsubstituted amino group, and
 pharmaceutically acceptable salts thereof.

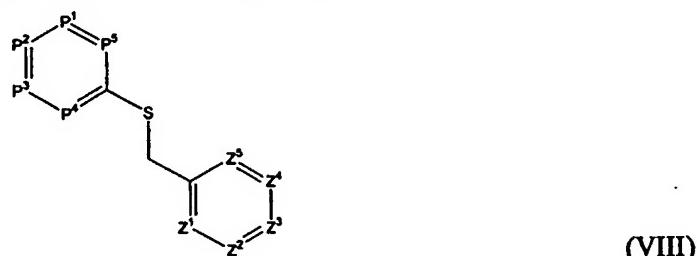
In another embodiment, the MC4-R binding compound is of formula (VII):



wherein

- Z¹, Z², Z³, Z⁴, and Z⁵ are CH, N, or substituted carbon; and
 15 P¹, P², P³, P⁴, and P⁵ are CH, N or substituted carbon.

In another embodiment, the MC4-R binding compound is of formula (VIII):

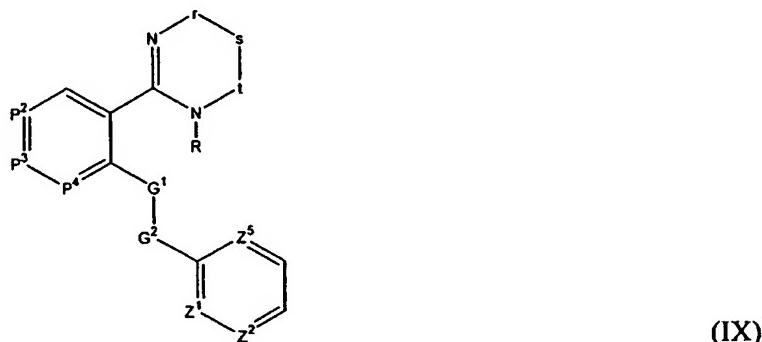


wherein

-6-

Z^1, Z^2, Z^3, Z^4 , and Z^5 are CH, N, or substituted carbon; and
 P^1, P^2, P^3, P^4 , and P^5 are CH, N or substituted carbon.

The invention also pertains to MC4-R binding compound of the formula (IX):



5 wherein:

P^2 is CH, CF, CCl, CBr, C-alkyl, C-alkoxy, C-CN, C-OH, or Cl;

P^3 is CH, CF, CCl, CBr, C-alkyl, C-alkoxy, C-CN, C-OH, or Cl;

P^4 is CH, CCl, CBr, CF, C-alkyl, C-alkoxy, C-CN, C-OH, or Cl;

G^1 and G^2 are each independently CH_2 , S, or O;

10 r is a covalent bond or CH_2 ;

t is CH_2 , CR^3 , or CR^3R^4 ;

s is CH_2 , CHR^5 or CR^5R^6 ;

R is hydrogen or alkyl;

Z^1 is CH, or covalently linked to Z^2 to form a naphthyl ring;

15 Z^2 is CH, C-(C≡CH), CCl, CBr, CI, CF, or covalently linked to Z^1 to form a naphthyl ring;

Z^5 is CH, or C-OMe;

R^3, R^4, R^5 , and R^6 are methyl, ethyl, hydroxyl, alkoxy, halogen, cyano, nitro, or amino, or pharmaceutically acceptable salts thereof.

20 The invention also features a pharmaceutical composition for the treatment of a MC4-R associated state in a mammal. The pharmaceutical compositions contain a pharmaceutically acceptable carrier and a MC4-R binding compound. The compounds are described herein in the context of the description of the method but it should be understood that the invention further pertains to pharmaceutical compositions containing 25 the compounds and the compounds *per se*. For example, pharmaceutical compositions of

-7-

the invention include a pharmaceutically acceptable carrier and an effective amount of at least one MC4-R binding compound of the formula (I):

B-Z-E (I)

5

wherein B is an anchor moiety, Z is a central moiety, E is a MC4-R interacting moiety, and pharmaceutically acceptable salts thereof.

Brief Description of the Drawings

- 10 Figures 1a and 1b are bar graphs showing the effects of MT II (a MC4-R agonist) on food intake in lean mice.

Figure 2 is a graph depicting the effects of treating lean mice with Compound N and MT II on food intake over a six hour period.

15

Figure 3 is a graph depicting the effects of treating lean mice with Compound O and MT II on food intake over a six hour period.

Detailed Description of the Invention

- 20 In one aspect, the invention pertains to a method for treating a melanocortin-4 receptor (MC4-R) associated state in a mammal. The method involves administering an effective amount of a MC4-R binding compound to a mammal, such that the MC4-R associated state is treated. The MC4-R binding compound is of the formula (I):

25

B-Z-E (I)

wherein B is an anchor moiety, Z is a central moiety, E is a MC4-R interacting moiety, and pharmaceutically acceptable salts thereof.

The term "MC4-R" includes receptors for α -melanocyte stimulating hormone.

- 30 The MC4-R is usually found in the brain where it is widely distributed (Mountjoy et al. *Mol. Endocrinol.* (1994) 8:1298-1308). Melanocortins are peptide hormones that play an important role in regulating melanocyte pigmentation as well as memory and

-8-

thermoregulation. They consist of various peptides, such as α -melanocyte stimulating hormone, that are cleaved from the polypeptide precursor proopiomelanocortin (POMC). The effects of melanocortins are mediated via stimulation of adenylate cyclase via the activation of the melanocortin receptors.

5 The melanocortin-4 receptor (MC4-R) is a G-protein coupled receptor (GPCR) expressed in brain tissue. The specific role of the MC4-R protein *in vivo* was investigated by engineering MC4-R "knock out" mice. The mice were unable to produce functional MC4-R protein, because the endogenous MC4-R gene coding sequence was deleted.

10 The knock-out mice were produced by using human MC4-r gene sequences to isolate and clone the murine MC4-r gene. A murine MC4-r targeting construct was then generated which was designed to delete the majority of the murine MC4-r coding sequence upon homologous recombination with the endogenous murine MC4-r gene. Embryonic stem (ES) cells containing the disrupted MC4-r gene were produced, isolated
15 and microinjected into murine blastocysts to yield mice chimeric for cells containing a disrupted MC4-r gene. Offspring of the chimeric mice resulting from germline transmission of the ES genome were obtained and animals heterozygous for the disrupted MC4-R were identified.

20 To assess the role of MC4-R *in vivo*, the animals heterozygous for the MC4-r disrupted gene were bred together, producing litters containing wild-type mice, mice heterozygous for the MC4-r mutation and mice homozygous for the MC4-R mutation. The weight gain of the animals was monitored regularly. Homozygous null MC4-R mutants showed an increase in weight compared to mice heterozygous for MC4-R deletion and wild type mice as early as 25 days of age. By 54-58 days of age, MC4-R deficient mice exhibited, on average, a 55-70% greater weight relative to wild type mice, and an approximately 50% greater weight compared to mice heterozygous for the MC4-R deletion.

25 The language "MC4-R associated states" includes those states, disorders, or diseases characterized by aberrant or undesirable activity or expression of MC4-Rs. It also includes those states, disorders and diseases associated with MC4-R ligands (e.g., α -melanocyte stimulating hormone). The language also includes prevention of states, disorders and diseases characterized by aberrant or undesirable activity of MC4-Rs or its

-9 -

ligands. Examples of MC4-R associated states include, but are not limited to, disorders involving pigmentation, weight homeostasis, e.g., weight loss or obesity. This can include the unhealthy decrease in body weight that can occur during an acute inflammatory response or that occurs in a cancer patient as a result of cachexia,
5 radiotherapy or chemotherapy, or to the undesirable decrease in body mass due to simulated or actual weightlessness, such as occurs during space travel.

Other examples of unhealthy decreases occur in some patients during advance stages of illnesses such as AIDS. Physiologically, this may be a result from any one of a number of complex factors, such as loss of appetite and possibly abnormal catabolism.
10 This cachexia, may be slowed by MC4-R binding compounds. In a preferred embodiment of the invention, the weight loss is a result of old age, anorexia nervosa, or cachexia (e.g., cachexia associated with cancer or HIV).

In one further embodiment, the MC4-R associated state is not weight loss.

The term "mammal" includes organisms which express the MC4-R. Examples
15 of mammals include mice, rats, cows, sheep, pigs, goats, horses, bears, monkeys, dogs, cats and, preferably, humans. Transgenic organisms which express the MC4-R are also included in this definition.

The language "MC4-R binding compound" includes those compounds which interact with the MC4-R resulting in modulation of the activity of the MC4-R. In an
20 embodiment, the MC4-R binding compounds are antagonists of the MC4-R. The term "antagonist" includes compounds which interact with the MC4-R and modulate, e.g., inhibit or decrease, the ability of a second compound, e.g., α -melanocyte stimulating hormone or another MC4-R ligand, to interact with the MC4-R. In another embodiment, the MC4-R binding compounds is an agonist of the MC4-R. The term
25 "agonists" includes compounds which interact with the MCR-4 and modulate, e.g., increase or stimulate, its activity and/or its ability to interact with a second compounds, e.g., α -melanocyte stimulaturing hormone.

MC4-R binding compounds can be identified through both *in vitro* (e.g., cell and non-cell based) and *in vivo* methods. These methods are described in detail in Examples
30 2, 3, 4, and 5.

The Scincillation Proximity Assay (SPA) is a non-cell based *in vitro* assay, described in Example 2. It can be used to identify compounds that interact with, e.g.,

-10-

bind to MC4-R. Such compounds may act as antagonists or agonists of MC4-R activity and may be used in the treatment of body weight disorders. One example of a qualitative measure of binding affinity of a MC4-R binding compound to MC4-R is its IC₅₀. Preferably, the MC4-R binding compound binds to the MC4-R with a binding 5 affinity, for example, of about 50μM or less, 20 μM or less, 10 μM or less, 5 μM or less, 2.5 μM or less, or 1 μM or less. In an advantageous embodiment, the IC₅₀ of a MC4-R binding compounds is about 0.5 μM or less, about 0.3 μM or less, about 0.1 μM or less, about 0.08 μM or less, about 0.06 μM or less, about 0.05 μM or less, about 0.04 μM or less, or, preferably, about 0.03 μM or less.

10 In the SPA, isolated membranes are used to identify compounds that interact with MC4-R. For example, in a typical experiment using isolated membranes, 293 cells may be genetically engineered to express the MC4-R. Membranes are harvested by standard techniques and used in an *in vitro* binding assay. ¹²⁵I-labeled ligand (e.g., ¹²⁵I-labeled α-MSH, β-MSH, or ACTH) is bound to the membranes and assayed for specific 15 activity; specific binding is determined by comparison with binding assays performed in the presence of excess unlabelled ligand.

To identify MC4-R binding compounds, membranes are incubated with labeled ligand in the presence or absence of test compound. Compounds that bind to the receptor and compete with labeled ligand for binding to the membranes reduced the 20 signal compared to the vehicle control samples. Preferably, the screens are designed to identify compounds that antagonize the interaction between MC4-R and MC4-R ligands such as α-MSH, β-MSH and ACTH. In such screens, the MC4-R ligands are labeled and test compounds can be assayed for their ability to antagonize the binding of labeled ligand to MC4-R.

25 Cell based assay systems can also be used to identify MC4-R binding compounds. An example of a cell based assay system is the cAMP assay described in detail in Example 3. Cell based methods may use cells that endogenously express MC4-R for screening compounds which bind to MC4-R. Alternatively, cell lines, such as 293 cells, COS cells, CHO cells, fibroblasts, and the like, genetically engineered to express 30 the MC4-R can also be used for screening purposes. Preferably, host cells genetically engineered to express a functional receptor that responds to activation by melanocortin peptides can be used as an endpoint in the assay; e.g., as measured by a chemical,

-11-

physiological, biological, or phenotypic change, induction of a host cell gene or a reporter gene, change in cAMP levels, adenylyl cyclase activity, host cell G protein activity, extracellular acidification rate, host cell kinase activity, proliferation, differentiation, etc.

- 5 To be useful in screening assays, the host cells expressing functional MC4-R should give a significant response to MC4-R ligand, preferably greater than 5-fold induction over background. Host cells should preferably possess a number of characteristics, depending on the readout, to maximize the inductive response by melanocortin peptides, for example, for detecting a strong induction of a CRE reporter
- 10 gene: (a) a low natural level of cAMP, (b) G proteins capable of interacting with the MC4-R, (c) a high level of adenylyl cyclase, (d) a high level of protein kinase A, (e) a low level of phosphodiesterases, and (f) a high level of cAMP response element binding protein would be advantageous. To increase response to melanocortin peptide, host cells could be engineered to express a greater amount of favorable factors or a lesser
- 15 amount of unfavorable factors. In addition, alternative pathways for induction of the CRE reporter could be eliminated to reduce basal levels.

In using such cell systems, the cells expressing the melanocortin receptor are exposed to a test compound or to vehicle controls (e.g., placebos). After exposure, the cells can be assayed to measure the expression and/or activity of components of the signal transduction pathway of the melanocortin receptor, or the activity of the signal transduction pathway itself can be assayed. For example, after exposure, cell lysates can be assayed for induction of cAMP. The ability of a test compound to increase levels of cAMP, above those levels seen with cells treated with a vehicle control, indicates that the test compound induces signal transduction mediated by the melanocortin receptor expressed by the host cell. In screening for compounds that may act as antagonists of MC4-R, it is necessary to include ligands that activate the MC4-R, e.g., α -MSH, β -MSH or ACTH, to test for inhibition of signal transduction by the test compound as compared to vehicle controls.

- When it is desired to discriminate between the melanocortin receptors and to
- 30 identify compounds that selectively agonize or antagonize the MC4-R, the assays described above may be conducted using a panel of host cells, each genetically engineered to express one of the melanocortin receptors (MC1-R through MC5-R).

-12-

Expression of the human melanocortin receptors is preferred for drug discovery purposes. To this end, host cells can be genetically engineered to express any of the amino acid sequences shown for melanocortin receptors 1 through 5. The cloning and characterization of each receptor has been described: MC1-R and MC2-R (Mountjoy., 5 1992, Science 257: 1248-1251; Chhajlani & Wikberg, 1992 FEBS Lett. 309: 417-420); MC3-R (Roselli-Rehfuss et al., 1993, Proc. Natl. Acad. Sci., USA 90: 8856-8860; Gantz et al., 1993, J. Biol. Chem. 268: 8246-8250); MC4-R (Gantz et al., 1993, J. Biol. Chem. 268: 15174-15179; Mountjoy et al., 1994, Mol. Endo. 8: 1298-1308); and MC5-R (Chhajlani et al., 1993, Biochem. Biophys. Res. Commun. 195: 866-873; Gantz et al., 10 1994, Biochem. Biophys. Res. Commun. 200: 1234-1220), each of which is incorporated by reference herein in its entirety. Thus, each of the foregoing sequences can be utilized to engineer a cell or cell line that expresses one of the melanocortin receptors for use in screening assays described herein. To identify compounds that specifically or selectively regulate MC4-R activity, the activation, or inhibition of MC4- 15 R activation is compared to the effect of the test compound on the other melanocortin receptors. In certain embodiments, it may be advantageous to select compounds of the invention selective for MC4-R, or, alternatively, it may be useful to select compounds which interact with other receptors as well.

In one further embodiment, the MC4-R binding compounds of the invention are 20 more selective for the MC4-R than at least one other MC receptors, for example, more than twice as selective, at least ten times as selective, at least twenty times as selective, at least fifty times as selective, or at least one hundred times as selective.

In one further embodiment, the MC4-R binding compounds of the invention are more selective for the MC4-R than the MC1-R, for example, more than twice as 25 selective, at least ten times as selective, at least twenty times as selective, at least fifty times as selective, or at least one hundred times as selective.

In one further embodiment, the MC4-R binding compounds of the invention are more selective for the MC4-R than the MC3-R, for example, more than twice as selective, at least ten times as selective, at least twenty times as selective, at least fifty 30 times as selective, or at least one hundred times as selective.

In one further embodiment, the MC4-R binding compounds of the invention are more selective for the MC4-R than the MC5-R, for example, more than twice as

-13 -

selective, at least ten times as selective, at least twenty times as selective, at least fifty times as selective, or at least one hundred times as selective.

In yet another further embodiment, the MC4-R binding compounds of the invention are more selective for the MC4-R receptor than at least one, two or three other 5 MC receptors (such as, for example, MC1-R, MC3-R, or MC5-R). In a further embodiment, the MC4-R binding compounds are more selective for the MC4-R than MC1-R, MC3-R, and MC5-R. In a further embodiment, the MC4-R binding compounds as at least ten times as selective, at least twenty times as selective, at least fifty times as selective, or at least one hundred times as selective for the MC4-R than the MC1-R, 10 MC3-R and the MC5-R.

As stated above, in an embodiment, the MC4-R binding compound includes compounds of the formula (I):



wherein B is an anchor moiety, Z is a central moiety, E is a MC4-R interacting 15 moiety, and pharmaceutically acceptable salts thereof.

The language "anchor moiety" ("B") includes moieties which interact with the MC4-R, which may, advantageously, result in the binding of the MC4-R binding compound to the MC4-R. Examples of anchor moieties include substituted or unsubstituted alkyl (e.g., branched, straight chain, or cyclic (e.g., cyclohexane, 20 cyclopentane)), alkenyl, alkynyl, aryl (e.g., substituted or unsubstituted phenyl, naphthyl, biphenyl, anthracenyl, fluorenyl, etc.), heterocyclic (e.g., thienyl, morpholinyl, piprazinyl, piperidinyl, etc.), and multicyclic (e.g., indolyl, benzothioenyl, etc.) moieties. Other examples of anchor moieties include carbonyl moieties, thiol groups, cyano groups, amino groups, and hydrogen atoms.

25 In a further embodiment, the anchor moiety ("B") includes substituted or unsubstituted carbocyclic aryl moieties, e.g., phenyl, naphthyl, etc. Examples of substituents include halogens (e.g., fluorine, chlorine, iodine, bromine, etc.), alkoxy (e.g., methoxy, ethoxy, isopropoxy, n-propoxy, n-butyloxy, pentoxy, cyclopentoxyl, arylalkyloxy, etc.) hydroxy, alkylcarbonyl, cyano, nitro, thiol, alkenyl, alkynyl (e.g., 30 ethynyl, etc.), alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, amino (including alkyl amino, dialkylamino,

-14-

- arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, trifluoromethyl, azido, heterocyclyl, alkylaryl, heteroaryl, alkyl (e.g., unsubstituted (e.g., methyl, ethyl, 5 propyl, butyl, hexyl, etc.) or substituted, e.g., halogen substituted, e.g., trifluoromethyl, trichloromethyl), aryl (e.g., substituted and unsubstituted phenyl, heteroaryl (e.g., thienyl, pyridinyl, etc.), arylalkyl, arylalkenyl, arylalkynyl, or combinations thereof. In yet another further embodiment, the anchor moiety substituent can be substituted itself with one or more halogen, nitro, alkyl, alkenyl, alkynyl, aryl or alkoxy groups, or 10 combinations thereof. In certain embodiments, the aryl moiety is fused to another ring which can be substituted or unsubstituted, carbocyclic or heterocyclic, aromatic or non-aromatic.

In a further embodiment, the anchor moiety is substituted with at least one halogen, alkoxy group, or alkyl (e.g., substituted or unsubstituted) group. Examples of 15 halogen substituted phenyl anchor moieties include *o*-iodophenyl, *m*-iodophenyl, *o*-bromophenyl, *m*-bromophenyl, *o*-chlorophenyl, *m*-chlorophenyl, *o*-fluorophenyl, *m*-fluorophenyl, *p*-fluorophenyl, *m*-nitrophenyl, or *o*-methoxy. The anchor moiety may also comprise more than one substituent, e.g. two halogens, e.g., two fluorines, a fluorine and a chlorine. Other examples of anchor moieties include 2-methoxy-5- 20 bromophenyl, 2-methoxy-5-fluorophenyl, 2-methoxy-5-iodophenyl, 2-methoxy-5-fluorophenyl, 2-ethoxy-5-bromophenyl, 2-methoxy-6-bromophenyl, 3-methoxy-6-bromophenyl, 2-isopropyl-5-bromophenyl, 2-*n*-propyl-5-bromophenyl, and 2-cyclopentyloxy-5-bromophenyl.

Other examples of anchor moieties include, but are not limited to, 2-methoxy-5- 25 cyanophenyl, 2-chloro-5-chlorophenyl, 2-methoxy-6-methoxyphenyl, 2-methoxy-5-nitrophenyl, 2-methoxy-5-phenyl phenyl, 2-methoxy-5-3'-thifuranyl phenyl, 2-methoxy-5-methylcarbonyl phenyl, 3,5-dimethyloxy phenyl, 2-methoxyphenyl, 2,5-dimethoxy phenyl, 2-fluoro-6-chlorophenyl, and 3-chloro-4-fluorophenyl.

In another further embodiment, the anchor moiety includes substituted and 30 unsubstituted heterocycles. Examples of such heterocycles include, but are not limited to, furanyl, imidazolyl, benzothiophenyl, benzofuranyl, quinolinyl, isoquinolinyl, benzodioxanyl, benzoxazolyl, benzothiazolyl, methylenedioxophenyl,

-15 -

ethylenedioxyphenyl, indolyl, thienyl, pyrimidyl, pyrazinyl, purinyl, deazapurinyl, morpholine, piprazine, piperidine, thiomorpholine, and thioazolidine. Examples of substituents include alkyl (e.g., substituted or unsubstituted, branched straight chain or cyclic, e.g., methyl, ethyl, propyl, butyl, pentyl, etc.), alkenyl, alkynyl, halogens (e.g., fluorine, chlorine, bromine, iodine, etc.), hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, 5 arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, azido, heterocyclyl, alkylaryl, aryl and heteroaryl groups.

In another further embodiment, the anchor moiety ("B") is a substituted or unsubstituted fused aryl or biaryl moiety. Biaryl moieties include moieties with two or 10 more aromatic rings, which may be fused or connected through one or more covalent bonds. Examples include biphenyl, fluorene, anthracenyl, benzoquinazolinyl, and naphthyl. Examples of substituents of biaryl moieties include alkyl (e.g., substituted and unsubstituted, branched or straight chain, methyl, ethyl, propyl, butyl, pentyl, etc.), alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, pentoxy, cyclopentoxy, etc.), alkenyl, 15 alkynyl, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, an aromatic 20 heteroaromatic moiety, halogens (e.g., fluorine, chlorine, bromine, iodine, etc.), combinations thereof and other groups which allow the MC4-R binding compound to perform its intended function. Biaryl moieties also include moieties which comprise one alkynyl, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, an aromatic 25 heteroaromatic moiety, halogens (e.g., fluorine, chlorine, bromine, iodine, etc.), combinations thereof and other groups which allow the MC4-R binding compound to perform its intended function. Biaryl moieties also include moieties which comprise one or more heterocycles, such as, benzothiofuranyl, benzothienyl, quinolinyl, benzothiophenyl, benzofuranyl, isoquinolinyl, benzodioxanyl, benzoxazolyl, benzothiazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, and indolyl. Examples of 30

-16-

biaryl anchor moieties include naphthyl, 2-methoxynaphthyl, 2-methoxy-5-phenyl phenyl, 2-ethoxynaphthyl, 2-methoxy-5-thiofuranyl phenyl, 2-methyl naphthyl, 2-n-propyl naphthyl, benxothiofuranyl, 2-phenyl phenyl, 2-methoxy-5-4'methoxy-phenyl phenyl; 2-methoxy-5-(3'-fluoro-4'-phenyl) phenyl phenyl; 2-cyclopentoxy naphthyl; 5 quinolinyl; and 2-methoxy-5-(3'-chloro-4'fluoro)phenyl phenyl.

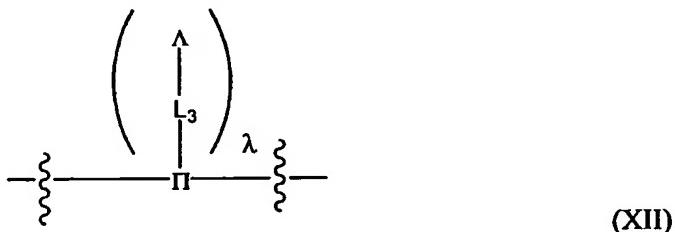
Furthermore, the anchor moiety can be multicyclic and comprise a combination of one or more aromatic, non-aromatic, heterocyclic, and heteroaryl rings, which can be fused, bridged, or linked together through covalent bonds. The multicyclic anchor moiety may also be substituted with substituents such as alkyl (e.g., substituted or 10 unsubstituted, branched straight chain or cyclic, e.g., methyl, ethyl, propyl, butyl, pentyl, etc.), alkenyl, alkynyl, halogens (e.g., fluorine, chlorine, bromine, iodine, etc.), hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl 15 amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, azido, heterocyclyl, alkylaryl, aryl and heteroaryl groups.

20 The term "central moiety" ("Z") includes moieties which covalently attach the anchor moiety to the MC4-R interacting moiety. Examples of central moieties include cyclic moieties, optionally substituted amines (e.g., tertiary amino, aminoalkylamino, dialkylaminoalkylamino, aminocarbonylamino, aminocarbonylamino; arylaminocarbonylamino groups; arylaminothiocarbonylamino), optionally substituted 25 alkyl groups (e.g., carbon atoms with substituted or unsubstituted alkyl, aryl (e.g., phenyl, naphthyl), heterocyclic moieties (e.g., morpholinyl, piprazinyl, etc.), and carbonyl groups, etc. Examples of substituents of the central moiety include, for example, alkyl (e.g., straight, branched or cyclic, substituted or unsubstituted, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), alkenyl (ethenyl, 30 propenyl, butenyl, etc.), alkynyl (e.g., ethynyl, propynyl, etc.), halogen (e.g., chlorine, fluorine, iodine, bromine), hydroxyl, alkoxy (e.g., methoxy, ethoxy, trifluoromethoxy, trichloromethoxy, propoxy, butoxy, cyclopropoxy, etc.), alkylcarbonyloxy,

-17-

arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, arylalkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, 5 arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, azido, heterocyclyl (e.g., morpholinyl, piprazinyl, etc.), arylalkyl, alkylaryl and aryl (e.g., substituted or unsubstituted phenyl (e.g., alkyl, halogen, alkoxy substituted), naphthyl, anthracene, etc.) and heteroaryl moieties. Furthermore, the 10 central moiety may further comprise one or more linking moieties. For example, the linking moieties may covalently link the cyclic moiety to the anchor moiety and/or the MC4-R interacting moiety.

The term "central moiety" also includes moieties of the formula (XII):



15 wherein

Π is a covalent bond, a carbon atom, a nitrogen atom, heterocyclic, alkyl, carbocyclic, or aryl;

20 L_3 is a covalent bond, C₁-C₆ branched, unbranched or cyclic alkyl (wherein one, two or three of the carbons are optionally replaced with oxygen, sulfur or nitrogen atoms), carbonyl, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, or aminothiocarbonyl moiety;

Λ is substituted or unsubstituted heterocyclic, aryl, alkoxy, amino, alkyl, alkenyl, alkynyl, or hydrogen; and

λ is 0, 1 or 2.

25 In a further embodiment, Π is a carbon or nitrogen atom. In other embodiments, Π is alkyl, carbocyclic, heterocyclic (e.g., piprazinyl, morpholinyl, piperidinyl, etc.).

In another further embodiment, Λ is heterocyclic (e.g., non-aromatic, e.g., substituted or unsubstituted, bridged, fused, or monocyclic, morpholinyl, piperidinyl,

-18-

azetidinyl, piprazinyl, etc. or aromatic, e.g., pyridinyl, pyrimidinyl, pyrrolyl, etc.), aryl e.g., phenyl, naphthyl) or amino (e.g., substituted or unsubstituted, e.g., alkylamino, dialkyl amino, etc.).

The language “cyclic moiety” includes heterocyclic and carbocyclic groups, such 5 as substituted or unsubstituted phenyl, heteroaryl, or biaryl moieties. Examples of cyclic moieties include those without aromaticity (e.g., cyclohexane, cyclopentane, etc.) and those with aromaticity, e.g. moieties that have at least one aromatic ring. Cyclic moieties may include one or more heteroatoms. Examples include phenyl, pyrrole, furan, thiophene, imidazole, benzoxazole, benzothiazole, triazole, tetrazole, pyrazole, 10 pyridine, pyrazine, pyridazine, pyrimidine, naphthyl, quinolyl, indolyl, and the like. The cyclic moiety can be substituted at one or more ring positions with such substituents such as, for example, alkyl (e.g., substituted or unsubstituted methyl, ethyl, propyl, butyl), alkenyl (ethenyl, propenyl, butenyl, etc.), alkynyl (e.g., ethynyl, propynyl, etc.), halogen (e.g., chlorine, fluorine, iodine, bromine), hydroxyl, alkoxy (e.g., methoxy, 15 ethoxy, trifluoromethoxy, trichloromethoxy, propoxy, butoxy, cyclopropoxy, etc.), aryloxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including 20 alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, azido, heterocyclyl, alkylaryl, and aryl (e.g., substituted or unsubstituted phenyl, naphthyl) and heteroaryl moieties. The cyclic moiety can also be fused or bridged with alicyclic or heterocyclic rings which are not 25 aromatic so as to form a polycycle (e.g., tetralin, or fluorene).

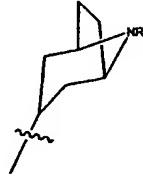
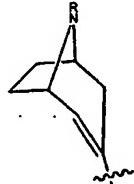
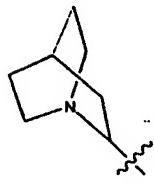
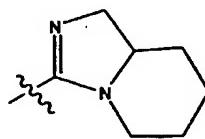
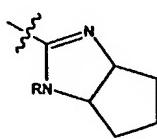
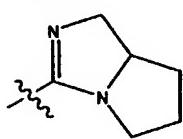
In an embodiment, the cyclic moiety of the present invention is substituted or unsubstituted phenyl, heteroaryl, or biaryl. The language “cyclic moiety” also includes non-aromatic cyclic moieties, such as, substituted or unsubstituted cyclic alkanes, (e.g., cyclohexane, and cyclopentane), cyclic alkenes (e.g., cyclohexene), and substituted or 30 unsubstituted heterocycles (e.g., thifuran, pyrimidine, pyrazine, pyrrole, imidazole, quinoxaline, etc.). The language “cyclic moiety” comprises not only the heterocyclic or carbocyclic moieties, but also may additionally include moieties which further comprise

-19-

linking moieties, such as L₁ and L₂ which, for example, may link the anchor moiety to the carbocyclic or heterocyclic cyclic portion of the cyclic moiety. Furthermore, linking moieties may also link the heterocyclic or carbocyclic cyclic moiety to the MC4-R interacting moiety. Examples of cyclic moieties include unsubstituted phenyl,
 5 halogenated phenyl (e.g., fluoro, bromo, chloro and iodo phenyl), alkyl substituted phenyl (e.g., methyl, ethyl, propyl, etc.), amino substituted phenyl, heteroaryls (e.g., thiofuran, pyridine, quinoxaline, pyrazine, pyrrole, etc.).

The language "MC4-R interacting moiety" ("E") includes moieties which permit the MC4-R binding compound to perform its intended function, e.g., interact with the
 10 MC4-R. Examples of MC4-R interacting moieties include substituted or unsubstituted alkyl (e.g., substituted with amino, cyano, nitro, hydroxy, etc.), aryl (e.g., phenyl, heteroaryl), amino (e.g., 3-aminopropylamino, dimethyl amino, diethyl amino), amidino, guanidino, carbocyclic and heterocyclic moieties. The language "MC4-R interacting moiety" is not intended to suggest that this moiety is the active pharmacophore of the
 15 molecule, responsible for the pharmacological, binding or other properties of the MC4-R binding compound.

In one embodiment, the MC4-R interacting moiety is cyclic, e.g., aryl, alkyl, biaryl, polycyclic, heteroaromatic, or heterocyclic. Examples of heterocyclic MC4-R interacting moieties include heterocycles which contain nitrogen atoms, such as,
 20 substituted and unsubstituted pyridinyl, pyrrolyl, piprazinyl, imidoazopyridinyl, pyrroloimidazolyl, pyrrolyl, azetidinyl, azapanyl, pyrimidinyl, pyridinyl, morpholinyl, diazapanyl, and piperidinyl moieties. The MC4-R interacting moiety may be bicyclic, polycyclic, bridged or a fused ring system. Examples of fused and bridged heterocycles include:



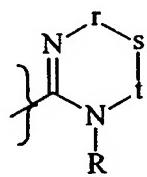
-20-

The substituent R includes substituted and unsubstituted alkyl (e.g., methyl, ethyl, etc.), benzocarbonyl, alkylcarbonyl, arylalkylcarbonyl, and other groups which allow the MC4-R interacting moiety to perform its intended function.

- The MC4-R interacting moiety can be substituted with substituents such as, but
- 5 not limited to, halogens (e.g., fluorine, chlorine, bromine, iodine, etc.), alkyl (e.g., substituted or unsubstituted, branched straight chain or cyclic, e.g., methyl, ethyl, propyl, butyl, pentyl, etc.), alkenyl, alkynyl, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato,
- 10 phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, aminoalkyl, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, azido, heterocyclyl, alkylaryl, aryl ,heteroaryl
- 15 moieties and combinations thereof.

In another embodiment, the MC4-R interacting moiety is not cyclic, e.g., the MC4-R interacting moiety is alkyl, unsubstituted amino, alkylamino, dialkylamino, amidino, guanidino, etc. Examples of alkyl MC4-R interacting moieties include straight and branched chain alkyls such as n-butyl, n-pentyl, and n-hexyl.

- 20 In another embodiment, the MC4-R interacting moiety contains one or more nitrogen atoms, e.g., pyridinyl, pyrrolyl, pyrazinyl, imidazolyl, quinoxalinyl, or pyrimidinyl. In a further embodiment, the MC4-R interacting moiety is of the formula (XIII):



(XIII)

- 25 wherein

r is a covalent bond, CH, CH₂, CR¹, CR¹R², or H;

t is CH, CH₂, CR³, CR³R⁴, or H;

s is CH, CH₂, CHR⁵, CR⁵R⁶, or absent;

-21 -

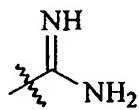
R is hydrogen, alkyl, alkenyl, arylalkyl, benzocarbonyl, arylalkylcarbonyl, alkylcarbonyl, optionally linked to A, B, L₁, L₂, R¹, R², R³, R⁴, R⁵, or R⁶ to form one or more rings;

R¹, R², R³, R⁴, R⁵, and R⁶ are each substituted or unsubstituted alkyl,

- 5 alkenyl, alkynyl, heterocyclic, halogen, thiol, hydroxyl, nitro, amino, cyano, or alkoxy, and may optionally be linked to form a carbocyclic or heterocyclic ring. The carbocyclic ring that is formed through the linkage of R, R¹, R², R³, R⁴, R⁵, or R⁶ may be bridged, fused, or spiro.

In one embodiment, the MC4-R interacting moiety is represented by the formula

- 10 (XIV) below, when s is absent:



(XIV)

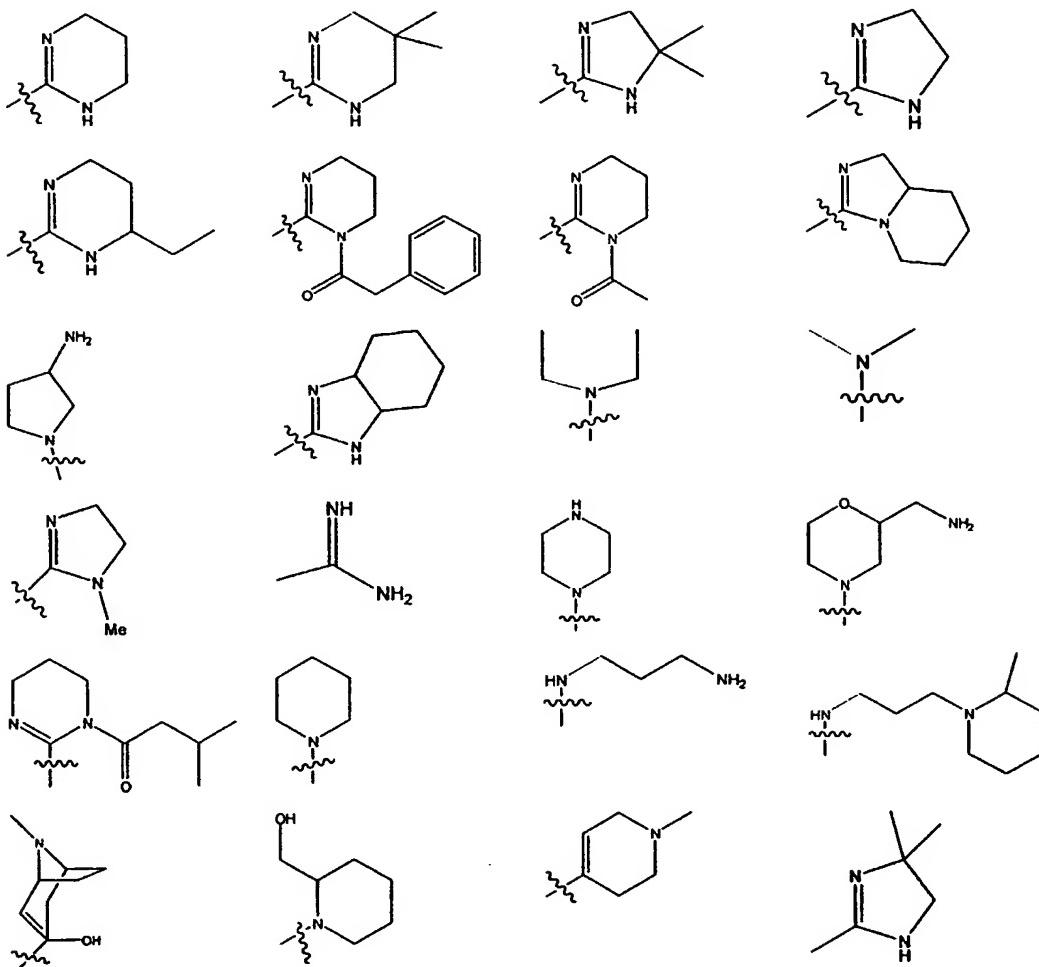
- For example, in another further embodiment, the MC4-R interacting moiety may be bicyclic, e.g., biheterocyclic, for example, quinoxaliny. The language "linked to form a ring" refers to moieties covalently connected through a chain of atoms (e.g., 15 carbon atoms and/or heteroatoms). The chain of atoms can comprise any number of atoms, which allow the MC4-R binding moiety to perform its intended function. In a further embodiment, the chain of atoms is selected such that a ring with three, four, five, six, seven, or eight members are formed. The ring that can be formed may be spiro (e.g., connected through the same carbon atom), fused (connected through adjacent 20 carbon atoms), or bridged (e.g., connected through carbon atoms which are neither identical nor adjacent). In an embodiment, R and t are linked, e.g., to for a bicyclic moiety. Examples of bicyclic moieties include, but are not limited to, imidazopyridinyl, pyrrolimidazolyl, cyclopentaimidazolyl, pyridopyrimidinyl, etc.

In a further embodiment R is H, alkyl, benzocarboxy, alkylcarboxy, or

- 25 arylalkylcarboxy. In another further embodiment, s is CR₅R₆ and R₅ and R₆ are each methyl. In another further embodiment, r is a covalent bond, and at least one of t and s are CH₂. In another, t, r, and s are each CH₂. In another, r is a covalent bond, and t and s are linked through a 4 carbon chain. In another further embodiment, at least one R group is OH.

-22 -

Examples of MC4-R interacting moieties include, but are not limited to, the following structures:



5 In another embodiment, the invention pertains to a method for treating an MC4-R associated state in a mammal, by administering an effective amount of a MC4-R binding compound to a mammal, such that the MC4-R associated state is treated. Examples of MC4-R binding compounds include compounds comprising the formula (II):

10

B-A-E

(II)

wherein:

B is a anchor moiety;

-23 -

A is a cyclic moiety; and
E is a MC4-R interacting moiety, and pharmaceutically acceptable salts thereof.

The MC4-R binding compounds of formula (II), may further comprise linking
5 moieties, L₁ and L₂. Such MC4-R binding compounds include compounds of the
formula (III):



wherein B is an anchor moiety (as described above), L₁ and L₂ are linking
moieties, A is a cyclic moiety (as described above), and E is a MC4-R interacting
10 moiety. Pharmaceutically acceptable salts of the MC4-R binding compound are also
included.

The language "linking moiety" includes moieties which link, preferably
covalently, the MC4-R interacting moiety, the cyclic moiety, and the anchor moiety of
the invention. Examples of linking moieties include covalent bonds, 1-10 atom chains
15 which may be branched or unbranched, substituted or unsubstituted alkyl, heterocyclic,
alkenyl, or alkynyl. The chains may be substituted with 0-3 heteroatoms or other
moieties which allow the MC4-R binding compound to perform its intended function.
Examples of suitable heteroatoms include sulfur, oxygen, nitrogen, and phosphorous.
The invention contemplates MC4-R binding compounds which comprises more than
20 two linking moieties.

In an embodiment, L₁ is a chain of 1-10 atoms (e.g., such as carbon, nitrogen,
oxygen, or sulfur atoms), e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 atoms. In an embodiment, L₁
is selected from the group consisting of a covalent bond, C₁-C₆, C₁-C₅, C₁-C₄, C₁-C₃, C₁-
15 C₂, branched or unbranched alkyl, wherein one, two or three of the carbons are
optionally replaced with oxygen, sulfur or nitrogen atoms. In a further embodiment, L₁
20 is a thioether (e.g., -S-CH₂-, S-CH(CH₃)-, -CH₂-S-CH₂, -S-, or -S-CH-(C₆H₅)-), an
ether (e.g., -O-CH₂ or -CH₂-O-CH₂-), a sulfoxide, a sulfone, an amine (e.g., -NH-, -NH-
CH₂-, -NMe-CH₂-, CH₂-NH-CH₂-, etc.) or alkyl (e.g., -CH₂-CH₂-, -CH₂-, or -CH₂-CH₂-
CH₂-). In another embodiment, L₁ comprises a sulfonyl group. Furthermore, L₁ can be
25 substituted or unsubstituted (e.g., a hydrogen can be replaced by another moiety), such
that the MC4-R binding compound is capable of performing its intended function, e.g.,
bind to or interact with the MC4-R. Examples of substituents include, but are not

-24 -

- limited to, halogens (e.g., fluorine, chlorine, bromine, iodine, etc.), alkyl (e.g., substituted or unsubstituted, branched straight chain or cyclic, e.g., methyl, ethyl, propyl, butyl, pentyl, etc.), alkenyl, alkynyl, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl,
- 5 alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro,
- 10 trifluoromethyl, azido, heterocyclyl, alkylaryl, aryl heteroaryl moieties, or combinations thereof.

In an embodiment, examples of L₂ include a covalent bond, a chain of 1-10 atoms (e.g., such as carbon, nitrogen, oxygen, or sulfur atoms), e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 atoms. In an embodiment, L₁ is selected from the group consisting of a covalent bond, C₁-C₆, C₁-C₅, C₁-C₄, C₁-C₃, C₁-C₂, branched or unbranched alkyl, wherein one, two or three of the carbons are optionally replaced with oxygen, sulfur or nitrogen atoms.. In a further embodiment, L₂ is a covalent bond, -CH₂- or -NH-. Furthermore, L₂ may also comprise one or more carbonyl groups. For example, L₂ linkers include substituted urea groups (NH-C=O-NH), oxycarbonylamino groups (-O-C=O-NH), 20 thiocarboynl groups, etc.

Furthermore, like L₁, L₂ can be substituted with any substituent such that the MC4-R binding compound is capable of performing its intended function. Examples of substituents include, but are not limited to, halogens (e.g., fluorine, chlorine, bromine, iodine, etc.), alkyl (e.g., substituted or unsubstituted, branched straight chain or cyclic, e.g., methyl, ethyl, propyl, butyl, pentyl, etc.), alkenyl, alkynyl, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl,

-25 -

sulfonamido, nitro, trifluoromethyl, azido, heterocycll, alkylaryl, aryl and heteroaryl moieties.

In a further embodiment, the MC4-R binding compound is of formula (III) (e.g., B-L₁-A-L₂-E), wherein B is substituted or unsubstituted biaryl (e.g., substituted or unsubstituted biphenyl, naphthyl, fluorenyl), unsubstituted or substituted heteroaryl (e.g., thieryl, benzothienyl, furanyl, pyrazinyl, pyrrolyl, pyrrolidinyl, etc.), unsubstituted or substituted phenyl, wherein one or more of said substituents are selected from the group consisting of halogens (e.g., bromine, fluorine, chlorine, iodine, etc.), alkyl groups (e.g., branched, straight chain or cyclic, substituted or unsubstituted, methyl, ethyl, propyl, butyl, etc.), alkoxy groups (e.g., substituted or unsubstituted alkoxy, e.g., methoxy, ethoxy, isopropoxy, n-propoxy, isobutoxy, n-butoxy, pentoxy, cyclopentoxy, methylenedioxy, ethylenedioxy, etc.), aryl groups (e.g., substituted or unsubstituted phenyl, heterocyclic groups), alkenyl, alkynyl, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, and azido;

L₁ is a covalent bond, C₁-C₁₀ branched or unbranched alkyl, wherein one or more of the carbons are optionally replaced with oxygen, sulfur or nitrogen atoms;

A is a substituted or unsubstituted phenyl, heteroaryl (e.g., pyrrolyl, pyrazinyl, pyridinyl, etc.), or biaryl (e.g., naphthyl, quinoxalinyl, purinyl, etc.) wherein said 25 substituent is selected from the group consisting of halogens (e.g., bromine, fluorine, chlorine, iodine, etc.), alkyl groups (e.g., branched, straight chain or cyclic, substituted or unsubstituted, methyl, ethyl, propyl, butyl, etc.), alkoxy groups (e.g., substituted or unsubstituted alkoxy, e.g., methoxy, ethoxy, isopropoxy, n-propoxy, isobutoxy, n-butoxy, pentoxy, cyclopentoxy, methylenedioxy, ethylenedioxy, etc.), aryl groups (e.g., substituted or unsubstituted phenyl, heterocyclic groups), alkenyl, alkynyl, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl,

-26 -

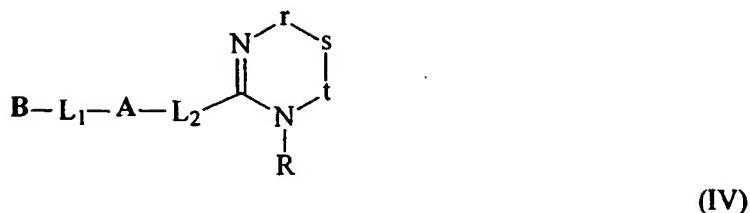
phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, 5 sulfonamido, nitro, trifluoromethyl, and azido;

L₂ is a covalent bond, a chain of 1-10 atoms (e.g., such as carbon, nitrogen, oxygen, or sulfur atoms), e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 atoms. In an embodiment, L₁ is selected from the group consisting of a covalent bond, C₁-C₆, C₁-C₅, C₁-C₄, C₁-C₃, C₁-C₂, branched or unbranched alkyl, wherein one, two or three of the carbons are 10 optionally replaced with oxygen, sulfur or nitrogen atoms, substituted or unsubstituted amino (e.g., -NH-, -NH-CH₂), ether, thioether, or alkyl (e.g., C₁-C₁₀, -CH₂-, -CH₂-CH₂-, or -CH₂-CH₂-CH₂-, etc.);

E is unsubstituted amino, unsubstituted and substituted alkylamino (e.g., 3-aminopropylamino), dialkylamino (e.g., dimethyl amino, diethyl amino), amidino, 15 guanidino, heterocyclic (e.g., substituted and unsubstituted piprazinyl, morpholinyl, piperidinyl, imidoazopyridinyl, pyrrolimidazolyl, pyridinyl, or pyrimidinyl) moieties, aryl (e.g., phenyl, heteroaromatic, e.g., substituted and unsubstituted pyrazinyl, imidazolyl, quinoxaliny, or pyrimidinyl), wherein said substituents include, but are not limited to, amino (e.g., unsubstituted amino, alkylamino, dialkyl amino), aminoalkyl 20 (e.g., methylamino, ethylamino, propylamino, etc.), alkyl (e.g., branched and straight chain, substituted and unsubstituted (e.g., carboxy, hydroxy, halogen, amino, cyano, nitro, etc. substituted), methyl, ethyl, propyl, butyl, etc.), aryl (e.g., phenyl, heteroaromatic), alkenyl (e.g., branched or straight chain, substituted or unsubstituted), alkynyl, etc, and pharmaceutically acceptable salts thereof.

25 In another embodiment, the invention pertains to a method for treating an MC4-R associated state in a mammal by administering an effective amount of a MC4-R binding compound to a mammal, such that the MC4-R associated state is treated. In an embodiment, the compound is of the formula (IV):

-27-



wherein

A is a substituted or unsubstituted phenyl, heteroaryl (e.g., pyrrolyl, pyrazinyl, pyridinyl, etc.), or biaryl (e.g., naphthyl, quinoxaliny, purinyl, etc.) wherein said

- 5 substituent is selected from the group consisting of halogens (e.g., bromine, fluorine, chlorine, iodine, etc.), alkyl groups (e.g., branched, straight chain or cyclic, substituted or unsubstituted, methyl, ethyl, propyl, butyl, etc.), alkoxy groups (e.g., substituted or unsubstituted alkoxy, e.g., methoxy, ethoxy, isopropoxy, n-propoxy, isobutoxy, n-butoxy, pentoxy, cyclopentox, methylenedioxy, ethylenedioxy, etc.), aryl groups (e.g.,
- 10 substituted or unsubstituted phenyl, heterocyclic groups), alkenyl, alkynyl, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including
- 15 alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, and azido;

- B is substituted or unsubstituted biaryl (e.g., substituted or unsubstituted biphenyl, naphthyl, fluorenyl), unsubstituted or substituted heteroaryl (e.g., thienyl,
- 20 benzothienyl, furanyl, pyrazinyl, pyrrolyl, pyrrolidinyl, etc.), unsubstituted or substituted phenyl, wherein one or more of said substituents are selected from the group consisting of halogens (e.g., bromine, fluorine, chlorine, iodine, etc.), alkyl groups (e.g., branched, straight chain or cyclic, substituted or unsubstituted, methyl, ethyl, propyl, butyl, etc.), alkoxy groups (e.g., substituted or unsubstituted alkoxy, e.g., methoxy, ethoxy, isopropoxy, n-propoxy, isobutoxy, n-butoxy, pentoxy, cyclopentox, methylenedioxy, ethylenedioxy, etc.), aryl groups (e.g., substituted or unsubstituted phenyl, heterocyclic groups), alkenyl, alkynyl, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxy carbonyl, alkylthiocarbonyl,
- 25 isopropoxy, n-propoxy, isobutoxy, n-butoxy, pentoxy, cyclopentox, methylenedioxy, ethylenedioxy, etc.), aryl groups (e.g., substituted or unsubstituted phenyl, heterocyclic groups), alkenyl, alkynyl, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxy carbonyl,

-28 -

aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, and azido;

L_1 and L_2 are selected from the group consisting of a covalent bond, C_1-C_4 branched or unbranched, substituted or unsubstituted alkyl, wherein one or two of the carbons are optionally replaced with oxygen, sulfur or nitrogen atoms;

r is a covalent bond, CH , CH_2 , CR^1 , CR^1R^2 , or H ;

10 t is CH , CH_2 , CR^3 , CR^3R^4 , or H ;

s is CHR_5 , CR_5R_6 or absent (e.g., leaving a non-cyclic diamine);

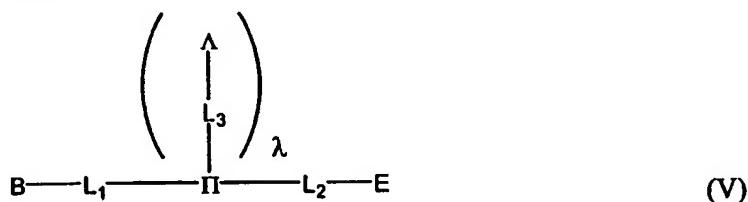
R is H, substituted or unsubstituted alkyl, arylalkyl, or heteroalkyl, and may optionally be linked to A, B, L₁, or L₂;

R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are each substituted or unsubstituted alkyl,

15 halogen, thiol, alkoxy, and may be optionally linked to each other to form additional ring moieties, e.g., quinoxalinyl. Pharmaceutically acceptable salts of the MC4-R binding compounds are also included.

In one further embodiment, A is substituted or unsubstituted phenyl. Examples of substituents include halogens (e.g., fluorine, chlorine, iodine, bromine), alkoxy, alkyl (e.g., methyl, trifluoromethyl), and amino moieties. In other embodiments, A is heteroaromatic, (e.g., thienyl), or biaryl, (e.g., napthyl or quinoxalinyl).

The invention also pertains to methods for treating an MC4-R associated state in a mammal comprising by administering an effective amount of a MC4-R binding compound of the formula (V):



25 B—L₁—H—L₂—E (V)
B is substituted or unsubstituted biaryl, unsubstituted or substituted heterocyclic, or unsubstituted or substituted phényl, wherein one or more of said substituents are halogens, alkyl, alkynyl, alkoxy, aryl, amino, cyano, or nitro;

-29 -

L_1 is a covalent bond, C_1-C_{10} branched or unbranched alkyl, wherein one or two of the carbons are optionally replaced with oxygen, sulfur or nitrogen atoms;

L_2 is a covalent bond, substituted or unsubstituted amino, ether, thioether, or alkyl;

5 E is substituted or unsubstituted alkyl, amino, amidino, guanidino, heterocyclic, or aryl, wherein said substituents are amino, arylalkyl, aminoalkyl, alkyl, aryl, alkenyl, or alkynyl;

Π is a covalent bond, a carbon atom, a nitrogen atom, heterocyclic, alkyl, carbocyclic, or aryl;

10 L_3 is a covalent bond, C_1-C_6 branched, unbranched or cyclic alkyl (wherein one, two or three of the carbons are optionally replaced with oxygen, sulfur or nitrogen atoms), carbonyl, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, or an aminothiocarbonyl moiety; and

15 Λ is substituted or unsubstituted heterocyclic, aryl, alkoxy, amino, alkyl, alkenyl, alkynyl, or hydrogen; and

λ is 0, 1 or 2, and pharmaceutically acceptable salts thereof.

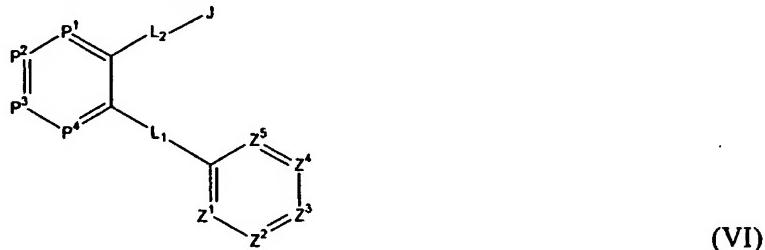
Examples of MC4-R binding compounds with this structure include, but are not limited to, compounds, wherein Π is a carbon atom, L_3 is aminocarbonyloxy, Λ is substituted aryl, λ is one, L_1 and L_2 are each CH_2 , and B and E are each pipridinyl.

20 Examples of substituents for Λ include but are not limited to, alkoxy (e.g., C_1-C_{10} alkoxy, e.g., methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptoxy, octoxy, nonoxy, and decoxy), cyano, halogens (e.g., fluorine, chlorine, bromine, iodine), alkyl (e.g., straight or branched chain, etc.), aryl, alkenyl, alkynyl, nitro, amino, or any other substituents which enables the MC4-R binding compound to perform its intended function, e.g., treat an MC4-R associated state.

Other examples of compounds of formula (V) include, but are not limited to, compounds wherein Π , L_2 and L_3 together are a single covalent bond, E is alkyl, and B is substituted or unsubstituted heterocyclic. In other compounds of formula (V), Π is a nitrogen atom, L_2 , L_1 and L_3 are each alkyl, E is substituted amino (e.g., alkyl substituted), or heterocyclic (e.g., piprazinyl, piperidinyl, morpholinyl, etc.) and B and Λ are each aryl (e.g., phenyl, anthracenyl, biaryl, e.g., naphthyl):

-30 -

In another further embodiment, the invention pertains to yet another method for treating an MC4-R associated state in a mammal by administering to a mammal an effective amount of a MC4-R binding compound of the formula(VI):



5 wherein

P^1, P^2, P^3 , and P^4 are optionally substituted carbon, sulfur, or nitrogen, and
wherein one of P^1, P^2, P^3 , and P^4 may represent a covalent bond;

Z^1, Z^2, Z^3, Z^4 , and Z^5 are optionally substituted carbon or nitrogen;

10 L^1 is a covalent bond, C₁-C₆ branched or unbranched alkyl, wherein one or two
of the carbons are optionally replaced with oxygen, sulfur or nitrogen atoms;

L_2 is a covalent bond, substituted or unsubstituted amino, ether, thioether, or
alkyl;

J is an unsubstituted or substituted nitrogen containing heterocycle or a
substituted or unsubstituted amino group, and pharmaceutically acceptable salts thereof.

15 Examples of substituents of $P^1, P^2, P^3, P^4, Z^1, Z^2, Z^3, Z^4$, and Z^5 include halogens
(e.g., bromine, fluorine, chlorine, iodine, etc.), alkyl groups (e.g., branched, straight
chain or cyclic, substituted or unsubstituted, methyl, ethyl, propyl, butyl, etc.), alkoxy
groups (e.g., substituted or unsubstituted alkoxy, e.g., methoxy, ethoxy, isopropoxy, n-
propoxy, isobutoxy, n-butoxy, pentoxy, cyclopentoxy, methylenedioxy, ethylenedioxy,
etc.), aryl groups (e.g., substituted or unsubstituted phenyl, heterocyclic groups),
alkenyl, alkynyl, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy,
aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxy carbonyl, aminocarbonyl,
alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl
amino, dialkylamino, arylamino, diarylamino, and alkylaryl amino), acylamino
20 (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino,
imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl,
sulfonamido, nitro, trifluoromethyl, and azido groups.

-31 -

In a further embodiment, P^1 , P^2 , P^3 , and P^4 are each substituted or unsubstituted carbon (e.g., CH). For example, P^1 and P^3 may be CH. In another further embodiment, P^2 and P^4 are each CH, CF, CCl, CBr, Cl, CMe, C-OMe, or C-OCF₃.

In a third further embodiment, Z^3 and Z^4 are each CH.

5 In a fourth further embodiment, Z^1 is CH, or covalently linked to Z^2 to form a naphthyl ring. Examples of Z^2 include CH, C-(C≡CH), CCl, CBr, Cl, and CF. Furthermore, Z^2 may be substituted with a chain of atoms which covalently links it to Z^1 to form a naphthyl ring.

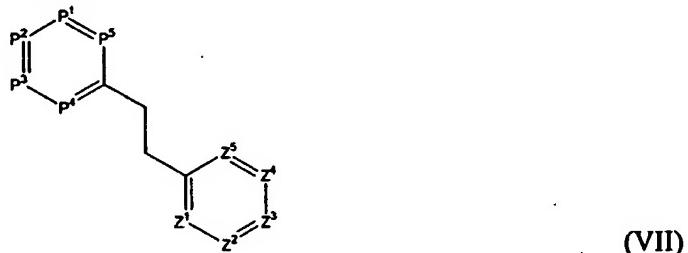
10 Examples of Z^5 include, but are not limited to, CH and C-alkoxy. The term "C-alkoxy" includes carbon atoms covalently bound to an alkoxy group, as described below. Examples of alkoxy groups include methoxy, ethoxy, propoxy, butoxy, etc.

In yet another further embodiment, L^2 is a covalent bond.

15 Examples of J include, but are not limited to, substituted or unsubstituted piprazinyl, imidoazopyridinyl, pyrroloimidazolyl, pyrrolyl, azetidinyl, azapanyl, diazapanyl, pyrimidinyl, pyridinyl, morpholinyl, or piperidinyl. Furthermore, J may be a substituted or unsubstituted fused ring or bridged heterocycle.

20 In a further embodiment, each of P^1 , P^2 , P^3 , and P^4 are each optionally substituted carbon; Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are each also optionally substituted carbon (e.g., alkoxy substituted, halogen substituted or linked to form a ring); wherein L_1 is either -S-CH₂- or CH₂-CH₂. In a further embodiment, L_2 is a covalent bond and J is a moiety of formula XIII, as described above.

In another embodiment, the MC4-R binding compound is of formula (VII):



wherein

25 Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are CH, N, or substituted carbon; and
 P^1 , P^2 , P^3 , P^4 , and P^5 are CH, N or substituted carbon.

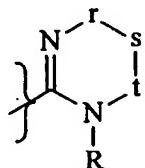
-32 -

Examples of substituents of Z^1 , Z^2 , Z^3 , Z^4 , Z^5 , P^1 , P^2 , P^3 , P^4 , and P^5 include halogens (e.g., bromine, fluorine, chlorine, iodine, etc.), alkyl groups (e.g., branched, straight chain or cyclic, substituted or unsubstituted, methyl, ethyl, propyl, butyl, etc.), alkoxy groups (e.g., substituted or unsubstituted alkoxy, e.g., methoxy, ethoxy, 5 isopropoxy, n-propoxy, isobutoxy, n-butoxy, pentoxy, cyclopentoxy, methylenedioxy, ethylenedioxy, etc.), aryl groups (e.g., substituted or unsubstituted phenyl, heterocyclic groups), alkenyl, alkynyl, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino 10 (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, and azido groups.

In a further embodiment, P^1 , P^2 , P^3 , P^4 and P^5 are each substituted or 15 unsubstituted carbon (e.g., CH). For example, P^1 and P^3 may be CH. In another further embodiment, P^2 and P^4 are each CH, CF, CCl, CBr, or Cl. Furthermore, P^1 , P^2 , P^3 , and P^4 can be linked covalently to form a bicyclic ring.

In a third further embodiment, Z^3 and Z^4 are each CH. 20 In a fourth further embodiment, Z^1 is CH, or covalently linked to Z^2 to form a naphthyl ring. Examples of Z^2 include CH, C-(C≡CH), CCl, CBr, CI, and CF. Furthermore, Z^2 may be substituted with a chain of atoms which covalently links it to Z^1 to form a naphthyl ring.

In a further embodiment, P^5 is C-L₂-J, wherein C is a carbon atom, L₂ is a linking moiety, e.g., a covalent bond, substituted or unsubstituted amino, ether, thioether, or 25 alkyl; and J is an unsubstituted or substituted nitrogen containing heterocycle or a substituted or unsubstituted amino group. In yet a further embodiment, L₂ is a covalent bond and J is a moiety of formula (XIII):



(XIII)

-33 -

wherein

r is a covalent bond, CH, CH₂, CR¹, CR¹R², or H;

t is CH, CH₂, CR³, CR³R⁴, or H;

s is CH, CH₂, alkenyl, CHR⁵, CR⁵R⁶, or absent;

5 R is hydrogen, alkyl, alkenyl, arylalkyl, benzocarbonyl,

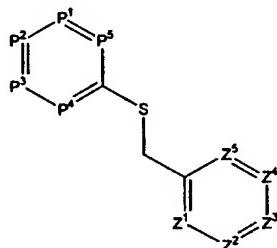
arylalkylcarbonyl, alkylcarbonyl, optionally linked to A, B, L₁, L₂, R¹, R², R³, R⁴, R⁵, or R⁶ to form one or more rings; and

10 R¹, R², R³, R⁴, R⁵, and R⁶ are each halogen, thiol, alkoxy, alkyl, alkenyl, alkynyl,

heterocyclic, hydroxyl, nitro, amino, cyano, aryl, optionally linked to form a ring with

15 R, R¹, R², R³, R⁴, R⁵, or R⁶.

In another embodiment, the MC4-R binding compound is of formula (VIII):



(VIII)

wherein

Z¹, Z², Z³, Z⁴, and Z⁵ are CH, N, or substituted carbon; and

15 P¹, P², P³, P⁴, and P⁵ are CH, N or substituted carbon.

Examples of substituents of Z¹, Z², Z³, Z⁴, Z⁵, P¹, P², P³, P⁴, and P⁵ include halogens (e.g., bromine, fluorine, chlorine, iodine, etc.), alkyl groups (e.g., branched, straight chain or cyclic, substituted or unsubstituted, methyl, ethyl, propyl, butyl, etc.), alkoxy groups (e.g., substituted or unsubstituted alkoxy, e.g., methoxy, ethoxy,

20 isopropoxy, n-propoxy, isobutoxy, n-butoxy, pentoxy, cyclopentoxo, methylenedioxy, ethylenedioxy, etc.), aryl groups (e.g., substituted or unsubstituted phenyl, heterocyclic groups), alkenyl, alkynyl, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy,

alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino

25 (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido),

-34 -

amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, and azido groups.

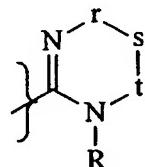
In a further embodiment, P¹, P², P³, and P⁴ are each substituted or unsubstituted carbon (e.g., CH). For example, P¹ and P³ may be CH. In another further embodiment, 5 P² and P⁴ are each CH, CF, CCl, CBr, or Cl. Furthermore, P¹, P², P³, and P⁴ can be linked covalently to form a bicyclic ring.

In a third further embodiment, Z³ and Z⁴ are each CH.

In a fourth further embodiment, Z¹ is CH, or covalently linked to Z² to form a naphthyl ring. Examples of Z² include CH, C-(C≡CH), CCl, CBr, Cl, and CF.

10 Furthermore, Z² may be substituted with a chain of atoms which covalently links it to Z¹ to form a naphthyl ring.

In a further embodiment, P⁵ is C-L₂-J, wherein C is a carbon atom, L₂ is a linking moiety, e.g., a covalent bond, substituted or unsubstituted amino, ether, thioether, or alkyl; and J is an unsubstituted or substituted nitrogen containing heterocycle or a 15 substituted or unsubstituted amino group. In yet a further embodiment, L₂ is a covalent bond and J is a moiety of formula (XIII):



(XIII)

wherein

r is a covalent bond, CH, CH₂, CR¹, CR¹R², or H;

20 t is CH, CH₂, CR³, CR³R⁴, or H;

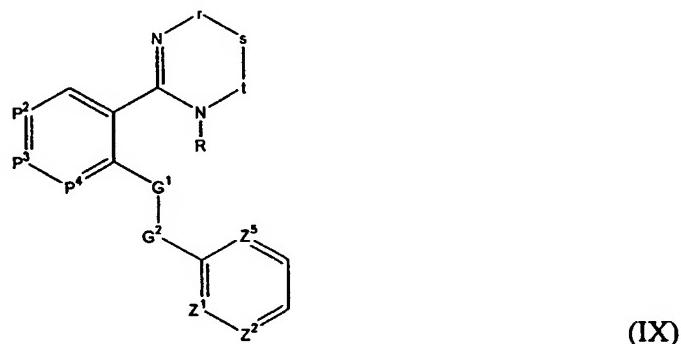
s is CH, CH₂, alkenyl, CHR⁵, CR⁵R⁶, or absent;

R is hydrogen, alkyl, alkenyl, arylalkyl, benzocarbonyl, arylalkylcarbonyl, alkylcarbonyl, optionally linked to A, B, L₁, L₂, R¹, R², R³, R⁴, R⁵, or 25 R⁶ to form one or more rings; and

R¹, R², R³, R⁴, R⁵, and R⁶ are each halogen, thiol, alkoxy, alkyl, alkenyl, alkynyl, heterocyclic, aryl, hydroxyl, nitro, amino, cyano, optionally linked to form a ring with R, R¹, R², R³, R⁴, R⁵, or R⁶.

-35 -

In another embodiment, the invention pertains to MC4-R binding compounds of formulae VII and VIII. Examples of MC4-R binding compound of these formulae include, for example, compounds wherein P⁵ is a carbon covalently bonded to a moiety of formula XIII. In a further embodiment, the moiety of formula XIII is not 5 benzoimidazole. In another further embodiment, Z³ is not ethoxy. In another embodiment, the invention pertains to both methods of using and MC4-R binding compounds of formula (IX):



wherein:

- 10 P² is CH, CF, CCl, CBr, C-alkyl, C-alkoxy, C-CN, C-OH, or Cl;
 - P³ is CH, CF, CCl, CBr, C-alkyl, C-alkoxy, C-CN, C-OH, or Cl;
 - P⁴ is CH, CCl, CBr, CF, C-alkyl, C-alkoxy, C-CN, C-OH, or Cl;
 - G¹ and G² are each independently CH₂, S, or O;
 - r is a covalent bond or CH₂;
 - 15 t is CH₂, CR³, or CR³R⁴;
 - s is CH₂, CHR⁵ or CR⁵R⁶;
 - R is hydrogen or alkyl;
 - Z¹ is CH, or covalently linked to Z² to form a naphthyl ring;
 - Z² is CH, C-(C≡CH), CCl, CBr, CI, CF, or covalently linked to Z¹ to 20 form a naphthyl ring;
 - Z⁵ is CH, or C-OMe;
 - R³, R⁴, R⁵, and R⁶ are methyl, ethyl, hydroxyl, alkoxy, halogen, cyano, nitro, amino, or pharmaceutically acceptable salts thereof.
- The language "linked to form a naphthyl ring" includes moieties which join Z¹ 25 and Z² to form a naphthyl (fused) ring system. Examples of such Z¹ and Z² groups include, but are not limited to, -CH=CH-CH=CH-.

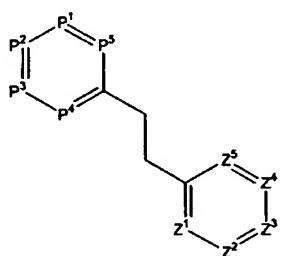
-36-

In a further embodiment, Z¹ is CH; Z² is CBr; and Z⁵ is C-OMe.

In another further embodiment, P² is CH. In another, P⁴ is CCl or CF. G¹ and G² are each CH₂. In another, G¹ and G² together are -CH₂-CH₂-, -CH₂-O-, -O-CH₂-, -CH₂-S- or -S-CH₂-. In another, Z¹ and Z² are linked to form a naphthyl ring.

5

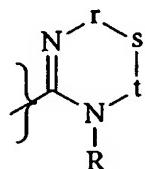
The invention pertains to MC4-R binding compound of the formula (VII):



(VII)

wherein

- 10 Z¹, Z², Z³, Z⁴, and Z⁵ are CH, N, or substituted carbon;
 P¹, P², P³, and P⁴ are CH, N or substituted carbon; and
 P⁵ is C-L₂-J, wherein L₂ is a covalent bond, alkyl (e.g., C₁-C₃), amino, ether,
 carbonyl, etc., and wherein J is a moiety of the formula (XIII):



(XIII)

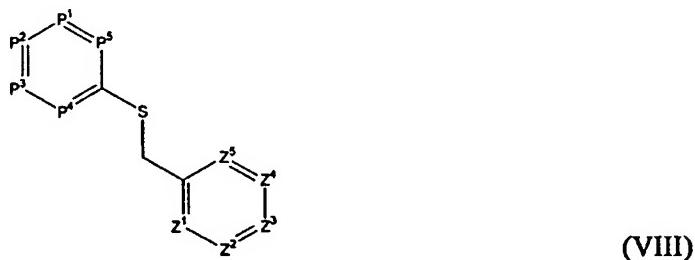
- 15 wherein

- r is a covalent bond, CH, CH₂, CR¹, CR¹R², or H;
 t is CH, CH₂, CR³, CR³R⁴, or H;
 s is CH, CH₂, CHR⁵, CR⁵R⁶, or absent;
 R is hydrogen, alkyl, alkenyl, arylalkyl, benzocarbonyl,
 20 arylalkylcarbonyl, alkylcarbonyl, optionally linked to R¹, R², R³, R⁴, R⁵, or R⁶ to form
 one or more rings; and

-37 -

R^1, R^2, R^3, R^4, R^5 , and R^6 are each halogen, thiol, alkoxy, alkyl, alkenyl, alkynyl, heterocyclic, hydroxyl, nitro, amino, cyano, aryl, optionally linked to form a ring with $R, R^1, R^2, R^3, R^4, R^5$, or R^6 .

5 The invention also pertains to MC4-R binding compound of the formula (VIII):



wherein

Z^1, Z^2, Z^3, Z^4 , and Z^5 are CH, N, or substituted carbon;
 10 P^1, P^2, P^3 , and P^4 are CH, N or substituted carbon; and
 P^5 is C-L₂-J, wherein L₂ is a covalent bond, alkyl (e.g., C₁-C₃), amino, ether, carbonyl, etc., and wherein J is a moiety of the formula (XIII):

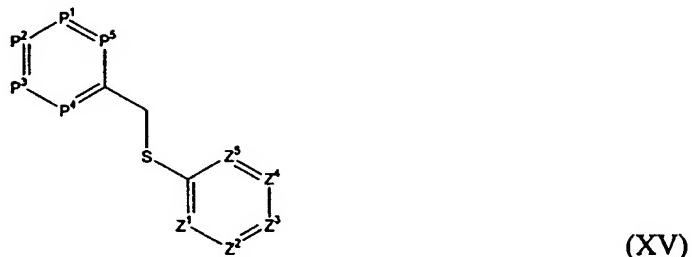


wherein

15 r is a covalent bond, CH, CH₂, CR¹, CR¹R², or H;
 t is CH, CH₂, CR³, CR³R⁴, or H;
 s is CH, CH₂, CHR⁵, CR⁵R⁶, or absent;
 R is hydrogen, alkyl, alkenyl, arylalkyl, benzocarbonyl, arylalkylcarbonyl, alkylcarbonyl, optionally linked to R¹, R², R³, R⁴, R⁵, or R⁶ to form
 20 one or more rings; and
 R^1, R^2, R^3, R^4, R^5 , and R^6 are each halogen, thiol, alkoxy, alkyl, alkenyl, alkynyl, heterocyclic, hydroxyl, nitro, amino, cyano, aryl, optionally linked to form a ring with $R, R^1, R^2, R^3, R^4, R^5$, or R^6 .

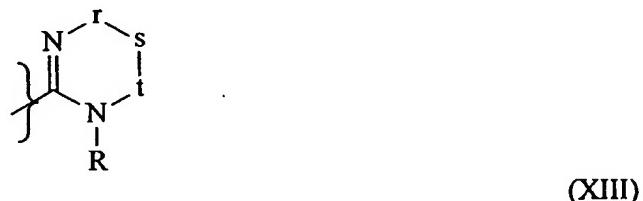
-38 -

The invention also pertains to MC4-R binding compound of the formula (XV):



wherein

- 5 Z^1, Z^2, Z^3, Z^4 , and Z^5 are CH, N, or substituted carbon;
 P^1, P^2, P^3 , and P^4 are CH, N or substituted carbon; and
 P^5 is C-L₂-J, wherein L₂ is a covalent bond, alkyl (e.g., C₁-C₃), amino, ether, carbonyl, etc., and wherein J is a moiety of the formula (XIII):

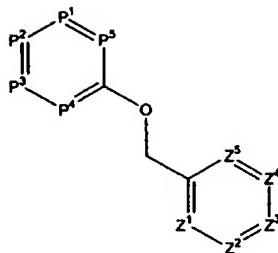


10 wherein

- r is a covalent bond, CH, CH₂, CR¹, CR¹R², or H;
t is CH, CH₂, CR³, CR³R⁴, or H;
s is CH, CH₂, CHR⁵, CR⁵R⁶, or absent;
R is hydrogen, alkyl, alkenyl, arylalkyl, benzocarbonyl,
15 arylalkylcarbonyl, alkylcarbonyl, optionally linked to R¹, R², R³, R⁴, R⁵, or R⁶ to form one or more rings; and
R¹, R², R³, R⁴, R⁵, and R⁶ are each halogen, thiol, alkoxy, alkyl, alkenyl, alkynyl, heterocyclic, hydroxyl, nitro, amino, cyano, aryl, optionally linked to form a ring with R, R¹, R², R³, R⁴, R⁵, or R⁶.

20 The invention also pertains to MC4-R binding compound of the formula (XVI):

-39-

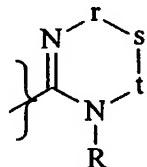


(XVI)

wherein

 Z^1, Z^2, Z^3, Z^4 , and Z^5 are CH, N, or substituted carbon; P^1, P^2, P^3 , and P^4 are CH, N or substituted carbon; and

- 5 P^5 is C-L₂-J, wherein L₂ is a covalent bond, alkyl (e.g., C₁-C₃), amino, ether, carbonyl, etc., and wherein J is a moiety of the formula (XIII):



(XIII)

wherein

r is a covalent bond, CH, CH₂, CR¹, CR¹R², or H;

- 10 t is CH, CH₂, CR³, CR³R⁴, or H;

s is CH, CH₂, CHR⁵, CR⁵R⁶, or absent;

15 R is hydrogen, alkyl, alkenyl, arylalkyl, benzocarbonyl, arylalkylcarbonyl, alkylcarbonyl, optionally linked to R¹, R², R³, R⁴, R⁵, or R⁶ to form one or more rings; and

- 20 R¹, R², R³, R⁴, R⁵, and R⁶ are each halogen, thiol, alkoxy, alkyl, alkenyl, alkynyl, heterocyclic, hydroxyl, nitro, amino, cyano, aryl, optionally linked to form a ring with R, R¹, R², R³, R⁴, R⁵, or R⁶.

In a further embodiment, the invention includes compounds wherein P¹, P², P³, and P⁴ of any one of formulas VII, VIII, XV, or XVI are each substituted or

- 25 unsubstituted carbon. For example, in one embodiment, P¹ is CH. In another example, at least one of P², P³ and P⁴ is a substituted carbon. In a further embodiment, P², P³ and P⁴ are selected from the group consisting of CH, CF, Cl, CBr, C-alkyl, C-alkyoxy, or CI.

-40-

In another embodiment, the compounds of formulae VII, VIII, XV, or XVI, include compounds wherein Z³ and Z⁴ are each CH. In another further embodiment of the formulae, Z¹ is CH. For example, in another further embodiment, Z¹ is covalently linked to Z² to form a naphthyl ring. Z² is CH, C-(C≡CH), CCl, CBr, Cl, and CF.

5 In another further embodiment, the compounds of the invention include compounds of formulae VII, VIII, XV, or XVI, wherein L₂ is a covalent bond. Also included are compounds wherein R is H, alkyl, benzocarboxy, alkylcarboxy, or arylalkylcarboxy.

10 In another further embodiment, the compounds of the invention include compounds of formulae VII, VIII, XV, or XVI, wherein s is CR₅R₆ and R₅ and R₆ are each methyl. In another example r is a covalent bond. Alternatively, each of t, r and s may be CH₂.

15 In one further embodiment, the MC4-R binding compounds of the invention of formula VII do not include benzoimadazole as the moiety of formula XIII, when P¹, P², P³, P⁴, Z¹, Z², Z⁴, Z⁵, and Z³ are each CH. Furthermore, in another further embodiment, the compounds of the invention do not include compounds wherein the moiety of formula XIII is tetrahydropyrimidine, when P¹, P², P³, P⁴, Z¹, Z², Z⁴, and Z⁵ are each CH and Z³ is C-OEt or CH.

20 In another further embodiment, the MC4-R binding compounds of the invention of formula VIII, do not include compounds wherein the moiety of formula XIII is benzoimidazolyl. In another further embodiment, the MC4-R binding compounds of the invention of formula VIII, do not include compounds wherein P² is not Cl, if P¹, P³, or P⁴ are CH. In another further embodiment, the MC4-R binding compounds of the invention of formula VIII, do not include compounds wherein P¹, P², P³, P⁴, Z¹, Z², Z⁴, Z³, and Z⁵ are each CH, when the moiety of formula XIII is tetrahydropyrimidine. In another further embodiment, the compounds of formula VIII of the invention do not include compounds wherein the moiety of formula is 4,5-dihydro-1H-imidazole, when P¹, P², P³, and P⁴ are each CH, and wherein one or two of Z¹, Z², or Z³ is CCl, and the remaining Z groups are CH. In another further embodiments, the MC4-R binding compounds of formula VIII of the invention, do not include compounds wherein the moiety of formula XIII is tetrahydropyrimidine, and when P¹, P², P³, and P⁴ are each CH, and Z² is CCl and the remaining Z groups are CH. In another further embodiments,

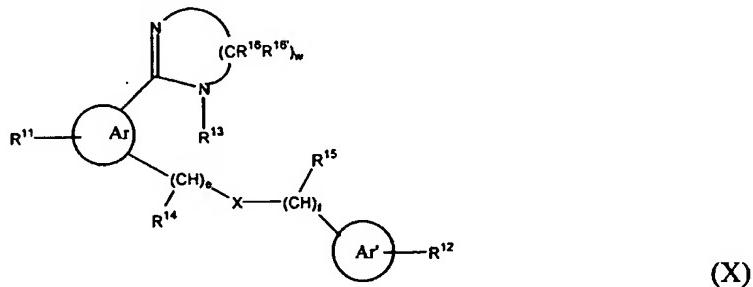
-41 -

the compounds of formula VIII of the invention, do not include compounds wherein when the moiety of formula XIII is tetrahydropyrimidine, and when P¹, P², P³, and P⁴ are each CH, and Z¹ and one of Z⁴ or Z⁵ are CCl and the remaining Z groups are CH.

In another further embodiment, the MC4-R binding compounds of the invention
5 do not include compounds of formula XV, wherein the moiety of formula VIII is not
benzimidazole if P¹, P², P³, P⁴ are each CH, and wherein Z² is CMe and the remaining
Z groups are CH.

In another further embodiment, the MC4-R binding compounds of the invention
do not include compounds of formula XVI, wherein the moiety of formula XVI, wherein
10 L₂ is not NH (e.g., amino), if P¹, P², P³, P⁴, Z¹, Z², Z⁴, Z⁵, and Z³ are each CH. In
another embodiment, the MC4-R binding compounds of formula XVI of the invention
do not include compounds wherein P groups are substituted to form a naphthyl ring.

In another embodiment, the invention features a method for treating an MC4-R
associated state in a mammal by administering an effective amount of a MC4-R binding
15 compound to a mammal. Compounds of formula (X) are also included in the invention.
In this embodiment, the compound is of the formula (X):



wherein

Ar and Ar' are aromatic groups;

20 R¹¹ is selected independently for each position capable of substitution
from the group hydrogen, cyano, nitro, alkoxy, halogen, alkyl, amino, or aryloxy.

R¹² is selected for each position capable of substitution from the group
consisting of hydrogen, halogen, alkoxy, acetylenic, nitro, aryl, alkyl, alkenyl, alkynyl,
cyano, acyl, or carbonyl;

25 R¹³ is hydrogen, alkenyl, alkynyl, aralkyl, nitro, cyano, alkyl (e.g., C₁-C₁₀)
alkyl, e.g., methyl, ethyl, etc.) acyl, carbonyl, or SO₂CH₃, and may optionally be linked
to an R¹⁶ or an R^{16'} group;

-42-

R^{16} and $R^{16'}$ are each independently selected for each position capable of substitution from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heterocyclic, carbonyl, or acyl, and may optionally be connected through an alkyl chain to R^{13} or another R^{16} or $R^{16'}$ group, to form a fused or spiro ring system;

5 X is NR^{17} , S, O or a covalent bond;

R^{17} is hydrogen, alkyl, alkenyl, alkynyl, acyl, heterocyclic, or carbonyl;

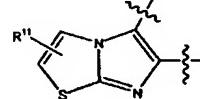
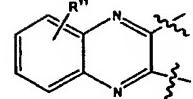
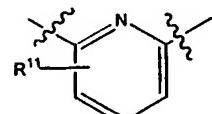
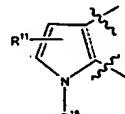
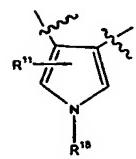
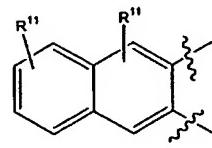
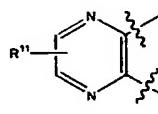
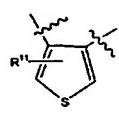
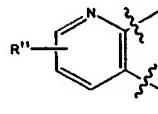
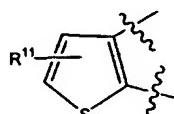
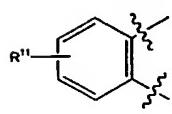
10 R^{14} and R^{15} are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, heteroaromatic, halogen, nitro, cyano, amino, or aryl, for each occurrence;

w is 0, 1, 2, 3, or 4;

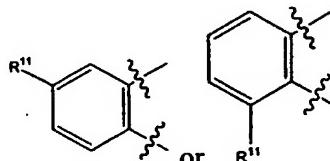
e is 0, 1, 2, or 3;

f is 0, 1, 2, or 3, and pharmaceutically acceptable salts thereof.

Examples of Ar groups include:



wherein R^{18} is acyl, alkyl or hydrogen.

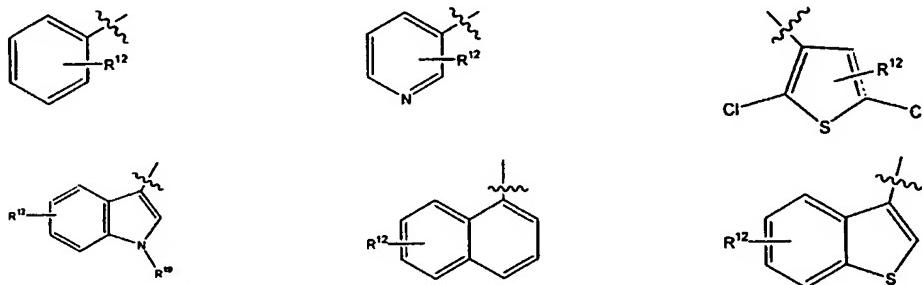


15 In a further embodiment, Ar is,

-43 -

R^{11} is selected independently for each aromatic position capable of substitution. Exemplary R^{11} groups include, but are not limited to, hydrogen, halogen (e.g., fluorine, chlorine, or bromine), alkyl, amino, and benzyloxy.

Examples of Ar' groups include:



5 wherein R^{19} is hydrogen, alkyl, acyl, aryl, alkenyl, or alkynyl.

In a further embodiment, each R^{12} group is selected independently from the group consisting of hydrogen, alkoxy, halogen (e.g., fluorine, bromine, chlorine, or iodine), and cyano. Examples of alkoxy groups include C₁-C₁₀ alkoxy, such as, methoxy, ethoxy, n-propoxy, i-propoxy, and cyclopentoxyl.

10 Examples of X include covalent bond, S, O and NR¹⁷. Examples of R¹⁷ include hydrogen, alkyl (e.g., C₁-C₁₀ alkyl, e.g., methyl), or acyl.

Examples of R¹⁶ and R^{16'} include alkyl and hydrogen. Each R¹⁶ and R^{16'} group is selected independently for each occurrence. In a further embodiment, at least one of R¹⁶ or R^{16'} are at least once hydrogen. In another embodiment, at least one of R¹⁶ or R^{16'}

15 are at least once C₁-C₁₀ alkyl, e.g., methyl or ethyl.

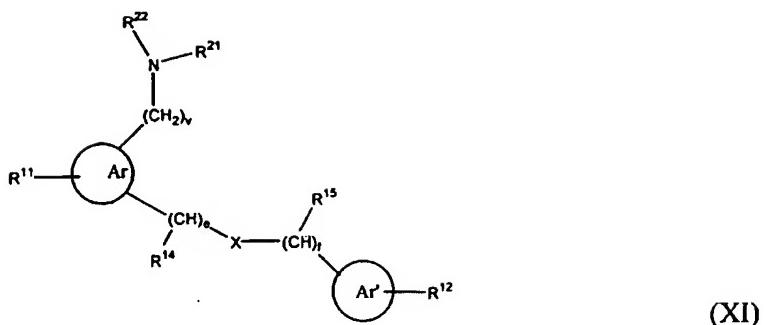
In yet another further embodiment, R¹⁴ and R¹⁵ are each independently hydrogen, alkyl (e.g., C₁-C₁₀, e.g., methyl) or phenyl for each occurrence.

20 In yet another further embodiment, R¹³ is hydrogen, acyl, alkyl (e.g., C₁-C₁₀ alkyl, e.g., methyl, ethyl, etc.) acyl, carboxy, or SO₂CH₃. Examples of acyl group include, but are not limited to, optionally substituted C₁-C₁₀alkyl acyl (e.g., i-propylcarbonyl and benzylcarbonyl).

In yet another further embodiment, w is 2 or 3. In yet another further embodiment, e is 0 or 1. In yet another further embodiment, f is 0 or 1.

25 In another embodiment, the invention features a method for treating an MC4-R associated state in a mammal by administering an effective amount of a MC4-R binding compound to a mammal. In this embodiment, the compound is of the formula (XI):

-44-



wherein

Ar and Ar' are aromatic groups, as described above;

R¹¹ is selected independently for each position capable of substitution

5 from the group hydrogen, halogen, alkyl, amino, cyano, or aryloxy.

R¹² is selected for each position capable of substitution from the group consisting of hydrogen, halogen, alkoxy, acetylenic, nitro, aryl, alkyl, alkenyl, alkynyl, cyano, acyl, or carbonyl;

X is NR¹⁷, S, O or a covalent bond;

10 R¹⁷ is hydrogen, alkyl, acyl, heterocyclic, or carbonyl;

R¹⁴ and R¹⁵ are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, or aryl, for each occurrence;

15 R²⁰ and R²¹ are each independently selected from the group consisting of substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, hydrogen, or carbonyl, and may optionally be linked to form a heterocycle (e.g., morpholinyl, piperazinyl, piperidinyl, etc.);

v is 0, 1, 2, 3, 4, 5, or 6;

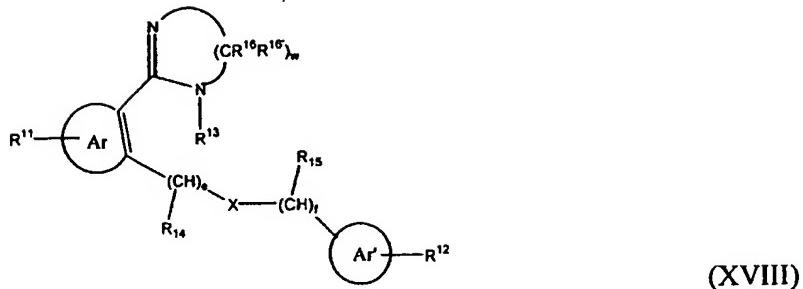
e is 0, 1, 2, or 3;

f is 0, 1, 2, or 3, and pharmaceutically acceptable salts thereof.

20 Examples of Ar, Ar', R¹¹, R¹², R¹⁴, R¹⁵ and X moieties include those described for formula (X).

Other examples of MC4-R binding compounds include compounds of the formula (XVIII):

-45-



wherein

Ar and Ar' are aromatic groups;

R¹¹ is selected independently for each position capable of substitution

5 from the group hydrogen, cyano, alkoxy, nitro, halogen, alkyl, amino, or aryloxy;

R¹² is selected for each position capable of substitution from the group consisting of hydrogen, halogen, alkoxy, acetylenic, nitro, aryl, alkyl, alkenyl, alkynyl, cyano, acyl, or carbonyl;

R¹³ is hydrogen, alkenyl, alkynyl, aralkyl, nitro, cyano, alkyl, acyl,

10 carbonyl, or SO₂CH₃, and may optionally be linked to an R¹⁶ or an R^{16'} group;

R¹⁶ and R^{16'} are each independently selected for each position capable of substitution from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, hydroxyl, cyano, aryl, heterocyclic, carbonyl, or acyl, and may optionally be connected through an alkyl chain to R¹³ or another R¹⁶ or R^{16'} group, to form a fused or spiro ring system;

15 X is NR¹⁷, S, O or a covalent bond;

R¹⁷ is hydrogen, alkyl, or carbonyl;

R¹⁴ and R¹⁵ are each independently hydrogen, halogen, or alkyl;

w is 1, 2, 3, or 4;

e is 0 or 1;

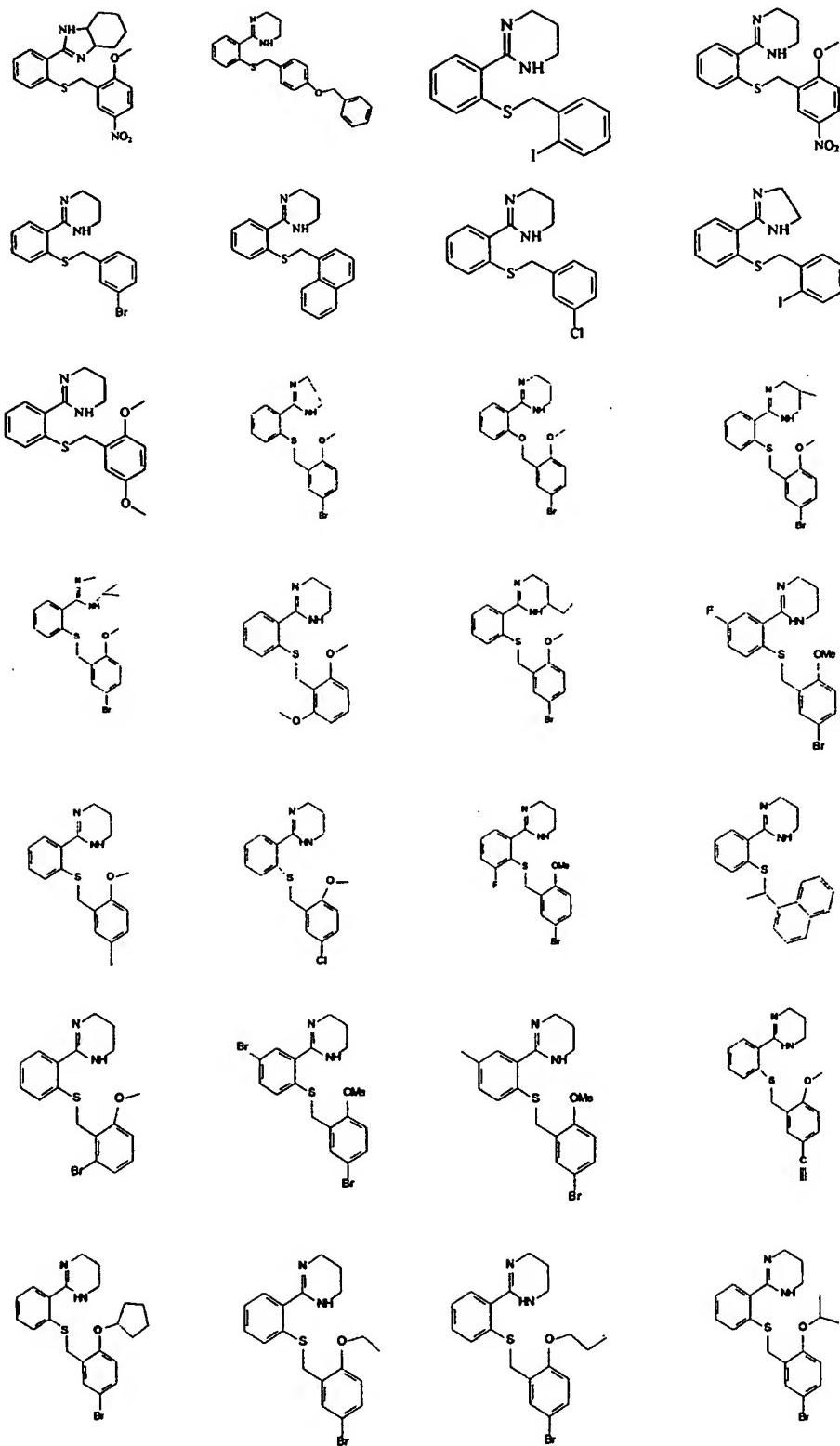
20 f is 0 or 1, wherein both e and f are not both 0 if X is a covalent bond, and pharmaceutically acceptable salts thereof.

Examples of Ar, Ar', R¹¹, R¹², R¹⁴, R¹⁵, R¹⁶ and R^{16'} and X moieties include those described for formula (X).

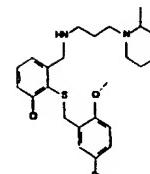
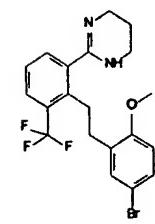
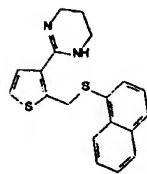
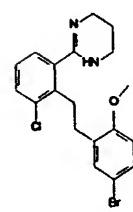
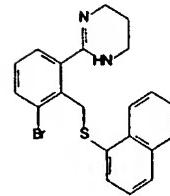
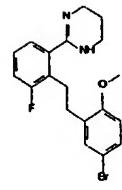
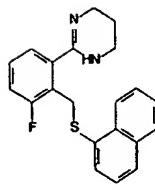
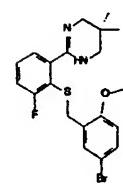
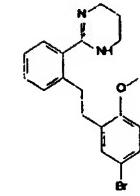
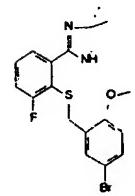
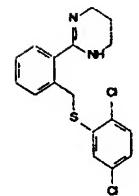
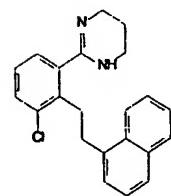
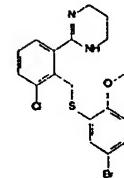
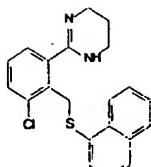
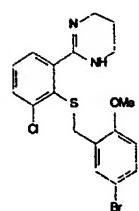
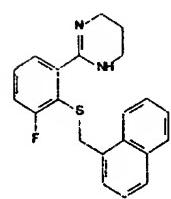
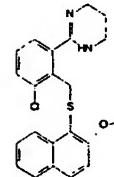
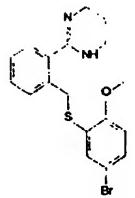
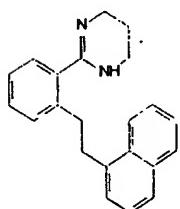
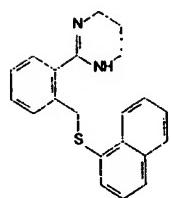
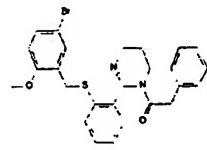
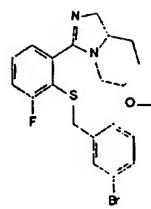
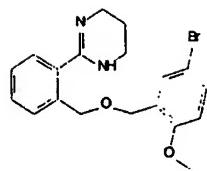
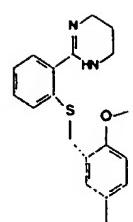
Other examples of MC4-R binding compounds include compounds of the

25 formulae:

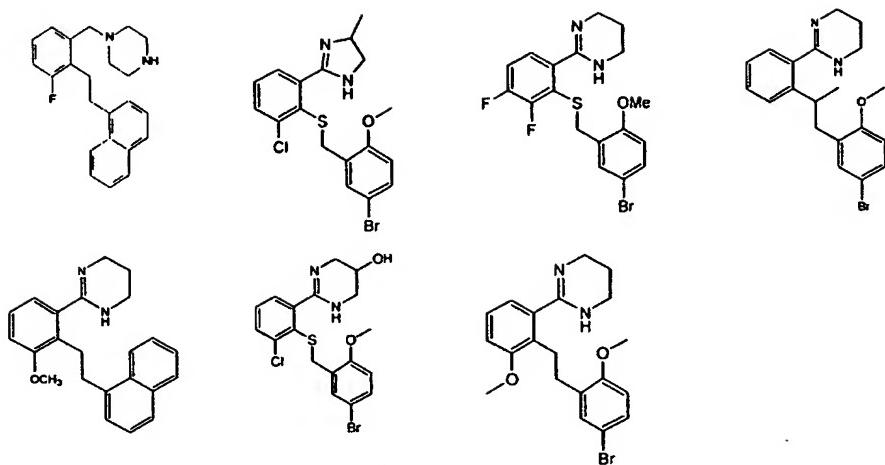
-46-



-47-



-48 -



The invention also includes MC4-R binding compounds such as:

- 2-[2-(4-benzyloxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-iodo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 5 2-[2-(2-methoxy-5-nitro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(3-chloro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2,5-dimethoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(3-bromo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 10 2-[2-(2-iodo-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
- 2-[2-(2-methoxy-5-nitro-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
- 2-[2-(2-methoxy-5-nitro-benzyloxy)-phenyl]-1,4,5,6-tetrahydropyrimidine;
- 2-[2-(2-bromo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(3-iodo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 15 2-[2-(2-methoxy-5-nitro-benzylsulfanyl)-phenyl]-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazole;
- 2-{2-[2-(2-methoxy-naphthalen-1-yl)-ethyl]-phenyl}-1,4,5,6-tetrahydropyrimidine;
- 2-[2-(5-bromo-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine;
- 2-{2-[2-(2-methyl-naphthalen-1-yl)-ethyl]-phenyl}-1,4,5,6-tetrahydropyrimidine;
- 20 2-{2-[2-(2,3-dihydro-benzo[1,4]dioxin-5-yl) -ethyl]-phenyl}-1,4,5,6-tetrahydropyrimidine;
- 2-[2-(2-methoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine;
- 2-(2-Benzylsulfanyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine;

-49 -

- 2-(2-Pentadecylsulfanyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine;
2-(2-Cyclohexylmethylsulfanyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Methyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(3-Nitro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
5 2-[2-(3,5-Dimethoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(4-Fluoro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Chloro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Fluoro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2,4-Bis-trifluoromethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
10 2-[2-(3-Methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(3,5-Bis-trifluoromethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Methoxy-5-nitro-benzyloxy)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
2-(2-Benzylsulfanyl-phenyl)-4,5-dihydro-1H-imidazole;
15 2-[2-(2,6-Difluoro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(Naphthalen-1-ylmethoxy)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
1-{2-[2-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-5,6-dihydro-4H-pyrimidin-1-yl}-
ethanone;
20 2-[2-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-3a,4,5,6,7,7a-hexahydro-1H-
benzoimidazole;
2-[2-(2-Iodo-benzylsulfanyl)-phenyl]-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazole;
2-[2-(2,5-Dimethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
4-[2-(1,4,5,6-Tetrahydro-pyrimidin-2-yl)-phenylsulfanyl]quinoline;
25 2-[2-(2-Methoxy-5-nitro-benzylsulfanyl)-pyridin-3-yl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Cyclopentyloxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2,3-Dihydro-benzo[1,4]dioxin-5-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
30 2-[2-(6-Methoxy-2,3-dihydro-benzo[1,4]dioxin-5-ylmethylsulfanyl)-phenyl]-1,4,5,6-
tetrahydro-pyrimidine;
2-[2-(5-fluoro-2-methoxy-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;

-50 -

- 1-Methyl-2-[2-(naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
2-[2-(5-Bromo-2-methoxy-benzyloxy)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(Naphthalen-1-yloxymethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
5 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-5,5-dimethyl-1,4,5,6-tetrahydro-
pyrimidine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-5,5-dimethyl-4,5-dihydro-1H-
imidazole;
2-[2-(2,6-Dimethoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
10 2-[2-(2-Bromo-6-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[5-Bromo-2-(5-bromo-2-methoxy-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
2-[5-Bromo-2-(5-bromo-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
2-[4-Bromo-2-(5-bromo-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
15 pyrimidine;
2-[2-(2-Bromo-5-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-5-methyl-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
2-[2-(Biphenyl-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
20 2-[2-(5-Chloro-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Methoxy-5-thiophen-3-yl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
2-[2-(Biphenyl-2-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(5-Iodo-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
25 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-5-fluoro-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
2-[2-(4,4'-Dimethoxy-biphenyl-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
30 pyrimidine;
2-[2-(9H-Fluoren-9-ylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;

-51 -

- 2-[2-(3'-Chloro-4'-fluoro-4-methoxy-biphenyl-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(1-Naphthalen-1-yl-ethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-5-fluoro-phenyl]-4,5-dihydro-1H-imidazole;
- 5 2-(2-Benzhydrylsulfanyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2'-Fluoro-4"-methoxy-[1,1';4',1"]terphenyl-3"-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzamidine;
- 2-[4-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 10 2-[2-(5-Ethynyl-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-cyclopentyloxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-ethoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 15 2-[2-(5-Bromo-2-propoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- [2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-diethyl-amine;
- 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-piperazine;
- C-{4-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-quinoxalin-2-yl]-morpholin-2-yl}-methylamine;
- 20 2-[2-(2-Methoxy-5-methyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzyloxymethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- [2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-dimethyl-amine;
- 2-[2-(5-Bromo-2-isopropoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Ethoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 25 2-[2-(2-Propoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 4-Methoxy-3-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenylsulfanylmethyl]-benzonitrile;
- 1-{4-Methoxy-3-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenylsulfanylmethyl]-phenyl}-ethanone;
- 30 2-[2-(Naphthalen-1-ylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-piperidine;

-52 -

- C-{4-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-morpholin-2-yl}-methylamine;
- 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-pyrrolidin-3-ylamine;
- 1-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-pyrrolidin-3-ylamine;
- 5 3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-1,5,6,7,8,8a-hexahydro-imidazo[1,5-a]pyridine;
- 3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-5,6,7,7a-tetrahydro-1H-pyrrolo[1,2-c]imidazole;
- 2-[2-(Benzo[b]thiophen-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 10 2-[3-Fluoro-2-(naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-(Naphthalen-1-ylmethylsulfanyl)-3-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenylamine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Methoxy-phenylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 15 1-{2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-5,6-dihydro-4H-pyrimidin-1-yl}-3-methyl-butan-1-one;
- 1-{2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-5,6-dihydro-4H-pyrimidin-1-yl}-2-phenyl-ethanone;
- 2-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-pyridin-2-yl]-1,4,5,6-tetrahydro-pyrimidine;
- 20 N-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-guanidine;
- 2-[2-(2-Isopropoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Cyclopentyloxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 25 (5-Bromo-2-methoxy-benzyl)-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenyl]-amine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Methoxy-naphthalen-1-ylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 30 2-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-pyrazin-2-yl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[3-Chloro-2-(naphthalen-1-ylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;

-53 -

- 2-[2-(6-Bromo-2-methoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[3-Chloro-2-(2-methoxy-naphthalen-1-ylsulfanyl)methyl]-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 5 2-[2-(5-Bromo-2-methoxy-phenylsulfanyl)methyl]-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-phenylsulfanyl)methyl]-3-chloro-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[1-(2-Naphthalen-1-yl-ethyl)-1H-pyrrol-2-yl]-1,4,5,6-tetrahydro-pyrimidine;
- 10 (5-Bromo-2-methoxy-benzyl)-methyl-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenyl]-amine;
- 2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzylamine;
- 2-[2-(2-Chloro-phenylsulfanyl)methyl]-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Bromo-phenylsulfanyl)methyl]-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 15 2-(2-o-Tolylsulfanyl)methyl-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2,5-Dichloro-phenylsulfanyl)methyl]-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-(3-Amino-propylamino)-6-(5-bromo-2-methoxy-benzylsulfanyl)-benzonitrile;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-1,4,5,6-tetrahydro-pyrimidine;
- [2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-diethyl-amine;
- 20 4-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-morpholine;
- 3'-(5-Bromo-2-methoxy-benzylsulfanyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl;
- 2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-piperazin-1-yl-6,7-dihydro-quinoxaline;
- 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-piperidine;
- C-{4-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-morpholin-2-yl}-
- 25 methylamine;
- 1-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-pyrazin-2-yl]-pyrrolidin-3-ylamine;
- 1-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-quinoxalin-2-yl]-pyrrolidin-3-ylamine;
- 1-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-pyrrolidin-3-ylamine;
- C-{4-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-pyrazin-2-yl]-morpholin-3-yl}-
- 30 methylamine;
- 1-[3-Fluoro-2-(2-naphthalen-1-yl-ethyl)-benzyl]-piperazine;
- 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-azetidine;

-54 -

- 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-pyrrolidin-3-ol;
[2-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 1-aza-bicyclo[2.2.2]oct-3-yl
ester;
[2-(2-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 1-aza-
5 bicyclo[2.2.2]oct-3-yl ester;
[2-(2-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 2-piperidin-1-yl-
ethyl ester;
{1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-pyrrolidin-2-yl}-
methanol;
10 4-tert-Butyl-N-naphthalen-1-ylmethyl-N-(2-piperidin-1-yl-ethyl)-benzamide;
N,N-Dimethyl-N'-naphthalen-2-ylmethyl-N'-naphthalen-1-ylmethyl-propane-1,3-
diamine;
N-(5-Bromo-2-methoxy-benzyl)-N',N'-dimethyl-N-naphthalen-1-ylmethyl-propane-1,3-
diamine;
15 1-Naphthalen-1-ylmethyl-3-phenethyl-1-(2-piperidin-1-yl-ethyl)-thiourea;
3-(4-Dimethylamino-phenyl)-1-(3-dimethylamino-propyl)-1-naphthalen-1-ylmethyl-
thiourea;
4-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzylamino]-piperidine-1-
carboxylic acid ethyl ester;
20 2-[2-(2-Naphthalen-1-yl-ethyl)-phenyl]-ethylamine;
Naphthalene-2-sulfonic acid (2-dimethylamino-ethyl)-naphthalen-1-ylmethyl-amide;
1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-2-methoxymethyl-
pyrrolidine;
(2-Hexyloxy-phenyl)-carbamic acid 2-piperidin-1-yl-1-piperidin-1-ylmethyl-ethyl ester;
25 3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyloxy]-pyrrolidine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyloxymethyl]-pyrrolidine;
2-[2-(Naphthalen-1-ylsulfanylmethyl)-phenyl]-piperidine;
3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzylamino]-propan-1-ol;
3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzylamino]-3-methyl-butan-1-ol;
30 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-pyrrolidin-3-ol;
{1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-pyrrolidin-2-yl}-methanol;
{1-[2-(Naphthalen-1-ylsulfanylmethyl)-benzyl]-piperidin-2-yl}-methanol;

-55 -

- 2-[2-(Naphthalen-1-ylsulfanylmethyl)-pyrrolidin-1-yl]-ethyl-N-pyrrolidine;
N-pyrrolyl-[1-(2-naphthalen-1-yl-ethyl)-pyrrolidin-2-ylmethyl]-amine;
1-(2-Naphthalen-1-yl-ethyl)-piperidine-2-carboxylic acid methyl ester;
(3-Bromo-benzyl)-(1-ethyl-pyrrolidin-2-ylmethyl)-naphthalen-1-ylmethyl-amine;
- 5 3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyloxy]-piperidine;
(5-Bromo-2-methoxy-benzyl)-(1-ethyl-pyrrolidin-2-ylmethyl)-naphthalen-1-ylmethyl-amine;
(1-Ethyl-pyrrolidin-2-ylmethyl)-naphthalen-2-ylmethyl-naphthalen-1-ylmethyl-amine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyloxymethyl]-pyrrolidine;
- 10 (3-Bromo-benzyl)-(3-imidazol-1-yl-propyl)-naphthalen-1-ylmethyl-amine;
(3-Imidazol-1-yl-propyl)-naphthalen-2-ylmethyl-naphthalen-1-ylmethyl-amine;
[2-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 2-piperidin-1-yl-1-piperidin-1-ylmethyl-ethyl ester;
[2-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 2-dimethylamino-ethyl ester;
- 15 1-[2-(Naphthalen-1-ylsulfanylmethyl)-benzyl]-piperazine;
[3-(2-Methyl-piperidin-1-yl)-propyl]-[2-(naphthalen-1-ylsulfanylmethyl)-benzyl]-amine;
1-[3-Chloro-2-(naphthalen-1-ylsulfanylmethyl)-benzyl]-piperazine;
N,N-Dimethyl-N'-(2-naphthalen-1-yl-ethyl)-N'-naphthalen-1-ylmethyl-ethane-1,2-
- 20 diamine;
{1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-piperidin-2-yl}-methanol;
1-[2-(2-Naphthalen-1-yl-ethyl)-benzyl]-piperazine;
[3-(2-Methyl-piperidin-1-yl)-propyl]-[2-(2-naphthalen-1-yl-ethyl)-benzyl]-amine;
1-[3-Fluoro-2-(2-naphthalen-1-yl-ethyl)-benzyl]-piperazine;
- 25 {1-[3-Chloro-2-(naphthalen-1-ylsulfanylmethyl)-benzyl]-piperidin-2-yl}-methanol;
{1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-piperidin-2-yl}-methanol;
{1-[2-(2-Naphthalen-1-yl-ethyl)-benzyl]-piperidin-2-yl}-methanol;
[3-(2-Methyl-piperidin-1-yl)-propyl]-[2-(2-naphthalen-1-yl-ethyl)-benzyl]-amine;
- 30 1-[2-(2-Naphthalen-1-yl-ethyl)-benzyl]-pyrrolidin-3-ylamine;
1-Phenyl-3-piperazin-1-yl-5,6,7,8-tetrahydro-isoquinoline-4-carbonitrile;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-6-ethyl-1,4,5,6-tetrahydro-pyrimidine;

-56 -

- 2-[2-(4-Methoxy-biphenyl-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Methoxy-5-phenylethynyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
2-[2-(2-Naphthalen-1-yl-ethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
5 2-[3-(2-Methoxy-naphthalen-1-ylsulfanylmethyl)-thiophen-2-yl]-1,4,5,6-tetrahydro-
pyrimidine;
2-[2-(2,5-Dimethoxy-phenylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(4-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-4,4-dimethyl-4,5-dihydro-
10 1H-imidazole;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-5,5-dimethyl-1,4,5,6-
tetrahydro-pyrimidine;
2-[3-(Naphthalen-1-ylsulfanylmethyl)-thiophen-2-yl]-1,4,5,6-tetrahydro-pyrimidine;
2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-phenyl}-1,4,5,6-tetrahydro-pyrimidine;
15 2-[3-Chloro-2-(2-naphthalen-1-yl-ethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-3-fluoro-phenyl}-1,4,5,6-tetrahydro-
pyrimidine;
2-[2-(5-Bromo-2-methoxy-phenylsulfanylmethyl)-3-fluoro-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
20 2-[2-(Naphthalen-1-ylsulfanylmethyl)-phenyl]-4,5-dihydro-1H-imidazole;
2-[3-Fluoro-2-(naphthalen-1-ylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[3-Bromo-2-(naphthalen-1-ylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-3-chloro-phenyl}-1,4,5,6-tetrahydro-
pyrimidine;
25 2-[2-(2-Methoxy-5-trifluoromethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
2-[4-(Naphthalen-1-ylsulfanylmethyl)-thiophen-3-yl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(Naphthalen-1-ylsulfanylmethyl)-thiophen-3-yl]-1,4,5,6-tetrahydro-pyrimidine;
2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-3-trifluoromethyl-phenyl}-1,4,5,6-
30 tetrahydro-pyrimidine;
2-[2-(2-Naphthalen-1-yl-ethyl)-3-trifluoromethyl-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(6-Fluoro-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;

-57 -

- {1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-piperidin-2-yl}-methanol;
2-[3-Fluoro-2-(2-naphthalen-1-yl-ethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-[3-(2-methyl-piperidin-1-yl)-
propyl]-amine;
- 5 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-pyrrolidin-3-ylamine;
1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-piperazine;
5,5-Dimethyl-2-[2-(2-naphthalen-1-yl-ethyl)-phenyl]-4,5-dihydro-1H-imidazole;
2-[3-Fluoro-2-(2-naphthalen-1-yl-ethyl)-phenyl]-5,5-dimethyl-4,5-dihydro-1H-
imidazole;
- 10 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3,5-difluoro-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3,5-difluoro-phenyl]-5,5-dimethyl-4,5-
dihydro-1H-imidazole;
3-(2-Naphthalen-1-yl-ethyl)-2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenylamine;
- 15 Amino-[2-(2-naphthalen-1-yl-ethyl)-phenyl]-acetonitrile;
1-[2-(2-Naphthalen-1-yl-ethyl)-phenyl]-ethane-1,2-diamine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-4-methyl-4,5-dihydro-1H-
imidazole;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-4-methyl-4,5-dihydro-1H-
imidazole;
- 20 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-phenyl]-4-methyl-4,5-dihydro-1H-
imidazole;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3,4-difluoro-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
- 25 2-[3-Fluoro-2-(naphthalen-1-ylsulfanyl)methyl)-phenyl]-5,5-dimethyl-4,5-dihydro-1H-
imidazole;
2-{2-[2-(5-Bromo-2-methoxy-phenyl)-1-methyl-ethyl]-phenyl}-1,4,5,6-tetrahydro-
pyrimidine;
- 30 2-[2-(5-Bromo-2-methoxy benzyl sulfanyl)-3-fluoro-4-trifluoromethyl-phenyl]-4,4-
dimethyl-4,5-dihydro-1H-imidazole;
2-[2-(5-Bromo-2-methoxy-benzyl sulfanyl)-3-fluoro-4-trifluoromethyl-phenyl]-5,5-
dimethyl-1,4,5,6-tetrahydro-pyrimidine;

-58 -

- 2-[3-Methoxy-2-(2-naphthalen-1-yl-ethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-phenyl]-1,4,5,6-tetrahydro-
pyrimidin-5-ol;
2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-3-methoxy-phenyl}-1,4,5,6-tetrahydro-
5 pyrimidine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-6-ethyl-1,4,5,6-tetrahydro-
pyrimidine, and pharmaceutically acceptable salts thereof.

Other compounds of the invention are shown in Table 4.

- In one further embodiment, the methods of the invention do not include methods
10 wherein 2-[2-(2,5-dichlorothiophen-3-ylmethylsulfanyl)-phenyl]-1, 4, 5, 6-
tetrahydropyrimidine (Compound A); 2[2-(2-chloro- 6-fluoro-benzylsulfanyl)-phenyl]-
1, 4, 5, 6-tetrahydropyrimidine (Compound B); 1-(6-bromo-2-chloro-quinolin-4-yl)-3-
(2-diethylaminoethyl)-urea (Compound AN); 2-[2-(2,6-difluorobenzylsulfanyl)-phenyl]-
1, 4, 5, 6-tetrahydropyrimidine (Compound AO); 1-(4-hydroxy-1, 3, 5-trimethyl-
15 piperadin-4-yl)-ethanone (Compound AR); 4,6-dimethyl-2-piperazin-1-yl-pyrimidine
(Compound FP); 2-piperazin-1-yl-pyrimidine (Compound FR); 1-pyridin-2-yl-
piperazine (Compound FS); 2-piperazin-1-yl-4-trifluoromethyl pyrimidine (Compound
FT); 6-piperazin-1-yl-7-trifluoromethyl-thieno[3,2-b]pyridine-3-carboxylic acid methyl
ester (Compound FU); 5-bromo-2-piperazin-1-yl)-pyrimidine (Compound FV); 1-(3-
20 trifluoromethyl-pyridin-2-yl)-piperazine (Compound FW); 1-(5-trifluoromethyl-pyridin-
2-yl)-piperazine (Compound FX); piperazine (Compound KY); or (2-Hexyloxy-phenyl)-
carbamic acid 2-piperidin-1-yl-1-piperidin-1-ylmethyl-ethyl ester (Compound OQ) are
used as MC4-R binding compounds. In another further embodiment, the compounds
claimed as MC4-R binding compounds do not include those listed above.

- 25 In another embodiment, the methods of the invention do not include methods
wherein 2-naphthalen-1-ylmethyl-4,5-dihydro-1H-imidazole (NAPHAZOLINE;
Compound AS); 10-[2-(1-methyl-piperadin-2-yl)-ethyl]-2-methylsulfanyl-10H-
phenothiazine (THORADIAZINE; THIODIAZINE; Compound AP); (2,6-dichloro-
phenyl)-imidazolidin-2-ylidene-amine (CLONIDINE; Compound AY); or 2-benzyl-4,5-
30 dihydro-1H-imidazole (TOLAZOLINE; Compound AZ) are used as MC4-R binding
compounds. In another further embodiment, the invention pertain to compounds other
than those listed above as MC4-R binding compounds.

-59-

In another further embodiment, the methods of the invention do not include 5-(4-chloro-phenyl)-2,5-dihydro-3H-imidazo[2,1-a]-isoindol-5-ol (MASPINDOL; Compound DT) as an MC4-R binding compound. In one embodiment, the compounds of the invention include MC4-R binding compounds other than MASPINDOL.

5 The term "alkyl" includes saturated aliphatic groups, including straight-chain alkyl groups (e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, etc.), branched-chain alkyl groups (isopropyl, tert-butyl, isobutyl, etc.), cycloalkyl (alicyclic) groups (cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl), alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. The term alkyl
10 further includes alkyl groups, which can further include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In an embodiment, a straight chain or branched chain alkyl has 10 or fewer carbon atoms in its backbone (e.g., C₁-C₁₀ for straight chain, C₃-C₁₀ for branched chain), and more preferably 6 or fewer. Likewise, preferred cycloalkyls have from 4-7 carbon atoms in
15 their ring structure, and more preferably have 5 or 6 carbons in the ring structure.

Moreover, the term alkyl includes both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy,
20 arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino,
25 arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Cycloalkyls can be further substituted, e.g., with the substituents described above. An "alkylaryl" or an "aralkyl" moiety is an alkyl
30 substituted with an aryl (e.g., phenylmethyl (benzyl)). The term "alkyl" also includes the side chains of natural and unnatural amino acids. Examples of halogenated alkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl,

-60 -

dichloromethyl, trichloromethyl, perfluoromethyl, perchloromethyl, perfluoroethyl, perchloroethyl, etc.

- The term "aryl" includes groups, including 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene,
- 5 phenyl, pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isooxazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like. Furthermore, the term "aryl" includes multicyclic aryl groups, e.g., tricyclic, bicyclic, e.g., naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, methylenedioxyphenyl, quinoline, isoquinoline,
- 10 napthridine, indole, benzofuran, purine, benzofuran, deazapurine, or indolizine. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles", "heterocycles," "heteroaryls" or "heteroaromatics". The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy,
- 15 alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino
- 20 (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (e.g.,
- 25 tetralin).

The term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond.

- For example, the term "alkenyl" includes straight-chain alkenyl groups (e.g.,
- 30 ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, etc.), branched-chain alkenyl groups, cycloalkenyl (alicyclic) groups (cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted

-61 -

cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. The term alkenyl further includes alkenyl groups which include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkenyl group has 6 or fewer 5 carbon atoms in its backbone (e.g., C₂-C₆ for straight chain, C₃-C₆ for branched chain). Likewise, cycloalkenyl groups may have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C₂-C₆ includes alkenyl groups containing 2 to 6 carbon atoms.

- Moreover, the term alkenyl includes both "unsubstituted alkenyls" and
- 10 "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl,
- 15 alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido,
- 20 nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond.

- 25 For example, the term "alkynyl" includes straight-chain alkynyl groups (e.g., ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, etc.), branched-chain alkynyl groups, and cycloalkyl or cycloalkenyl substituted alkynyl groups. The term alkynyl further includes alkynyl groups which include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon 30 backbone. In certain embodiments, a straight chain or branched chain alkynyl group has 6 or fewer carbon atoms in its backbone (e.g., C₂-C₆ for straight chain, C₃-C₆ for

-62 -

branched chain). The term C₂-C₆ includes alkynyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkynyl includes both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents 5 replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxyacarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxyacarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, 10 phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or 15 heteroaromatic moiety.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to five carbon atoms in its backbone structure. "Lower alkenyl" and "lower alkynyl" have chain lengths of, for example, 2-5 carbon atoms.

20 The term "acyl" includes compounds and moieties which contain the acyl radical (CH₃CO-) or a carbonyl group. The term "substituted acyl" includes acyl groups where one or more of the hydrogen atoms are replaced by for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxyacarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxyacarbonyl, 25 aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, 30 nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

-63 -

The term "acylamino" includes moieties wherein an acyl moiety is bonded to an amino group. For example, the term includes alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

The term "aroyl" includes compounds and moieties with an aryl or
5 heteroaromatic moiety bound to a carbonyl group. Examples of aroyl groups include phenylcarboxy, naphthyl carboxy, etc.

The terms "alkoxyalkyl", "alkylaminoalkyl" and "thioalkoxyalkyl" include alkyl groups, as described above, which further include oxygen, nitrogen or sulfur atoms replacing one or more carbons of the hydrocarbon backbone, e.g., oxygen, nitrogen or
10 sulfur atoms.

The term "alkoxy" includes substituted and unsubstituted alkyl, alkenyl, and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups include methoxy, ethoxy, isopropoxy, propoxy, butoxy, and pentoxy groups and may include cyclic groups such as cyclopentoxy. Examples of substituted alkoxy groups
15 include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino
20 (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted
25 alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, etc.

The term "amine" or "amino" includes compounds where a nitrogen atom is covalently bonded to at least one carbon or heteroatom. The term "alkyl amino" includes groups and compounds wherein the nitrogen is bound to at least one additional
30 alkyl group. The term "dialkyl amino" includes groups wherein the nitrogen atom is bound to at least two additional alkyl groups. The term "aryl amino" and "diaryl amino" include groups wherein the nitrogen is bound to at least one or two aryl groups,

-64 -

respectively. The term "alkylarylamino," "alkylaminoaryl" or "arylaminooalkyl" refers to an amino group which is bound to at least one alkyl group and at least one aryl group. The term "alkaminooalkyl" refers to an alkyl, alkenyl, or alkynyl group bound to a nitrogen atom which is also bound to an alkyl group.

- 5 The term "amide" or "aminocarboxy" includes compounds or moieties which contain a nitrogen atom which is bound to the carbon of a carbonyl or a thiocarbonyl group. The term includes "alkaminocarboxy" groups which include alkyl, alkenyl, or alkynyl groups bound to an amino group bound to a carboxy group. It includes arylaminocarboxy groups which include aryl or heteroaryl moieties bound to an amino group which is bound to the carbon of a carbonyl or thiocarbonyl group. The terms "alkylaminocarboxy," "alkenylaminocarboxy," "alkynylaminocarboxy," and "arylaminocarboxy" include moieties wherein alkyl, alkenyl, alkynyl and aryl moieties, respectively, are bound to a nitrogen atom which is in turn bound to the carbon of a carbonyl group.
- 10 The term "carbonyl" or "carboxy" includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom, and tautomeric forms thereof. Examples of moieties which contain a carbonyl include aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, etc. The term "carboxy moiety" or "carbonyl moiety" refers to groups such as "alkylcarbonyl" groups wherein an alkyl group is covalently bound to a carbonyl group, "alkenylcarbonyl" groups wherein an alkenyl group is covalently bound to a carbonyl group, "alkynylcarbonyl" groups wherein an alkynyl group is covalently bound to a carbonyl group, "arylcarbonyl" groups wherein an aryl group is covalently attached to the carbonyl group. Furthermore, the term also refers to groups wherein one or more heteroatoms are covalently bonded to the carbonyl moiety. For example, the term includes moieties such as, for example, aminocarbonyl moieties, (wherein a nitrogen atom is bound to the carbon of the carbonyl group, e.g., an amide), aminocarbonyloxy moieties, wherein an oxygen and a nitrogen atom are both bond to the carbon of the carbonyl group (e.g., also referred to as a "carbamate"). Furthermore, aminocarbonylamino groups (e.g., ureas) are also included as well as other combinations of carbonyl groups bound to heteroatoms (e.g., nitrogen, oxygen, sulfur, etc. as well as carbon atoms). Furthermore, the heteroatom can be
- 15
- 20
- 25
- 30

-65 -

further substituted with one or more alkyl, alkenyl, alkynyl, aryl, aralkyl, acyl, etc. moieties.

- The term "thiocarbonyl" or "thiocarboxy" includes compounds and moieties which contain a carbon connected with a double bond to a sulfur atom. The term
- 5 "thiocarbonyl moiety" includes moieties which are analogous to carbonyl moieties. For example, "thiocarbonyl" moieties include aminothiocarbonyl, wherein an amino group is bound to the carbon atom of the thiocarbonyl group, furthermore other thiocarbonyl moieties include, oxythiocarbonyls (oxygen bound to the carbon atom), aminothiocarbonylamino groups, etc.

- 10 The term "ether" includes compounds or moieties which contain an oxygen bonded to two different carbon atoms or heteroatoms. For example, the term includes "alkoxyalkyl" which refers to an alkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom which is covalently bonded to another alkyl group.

- 15 The term "ester" includes compounds and moieties which contain a carbon or a heteroatom bound to an oxygen atom which is bonded to the carbon of a carbonyl group. The term "ester" includes alkoxy carboxy groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxy carbonyl, etc. The alkyl, alkenyl, or alkynyl groups are as defined above.

- 20 The term "thioether" includes compounds and moieties which contain a sulfur atom bonded to two different carbon or hetero atoms. Examples of thioethers include, but are not limited to alkthioalkyls, alkthioalkenyls, and alkthioalkynyls. The term "alkthioalkyls" include compounds with an alkyl, alkenyl, or alkynyl group bonded to a sulfur atom which is bonded to an alkyl group. Similarly, the term "alkthioalkenyls" and alkthioalkynyls" refer to compounds or moieties wherein an alkyl, alkenyl, or
- 25 alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkynyl group.

The term "hydroxy" or "hydroxyl" includes groups with an -OH or -O⁻.

- 30 The term "halogen" includes fluorine, bromine, chlorine, iodine, etc. The term "perhalogenated" generally refers to a moiety wherein all hydrogens are replaced by halogen atoms.

The terms "polycyclyl" or "polycyclic radical" include moieties with two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls)

-66 -

in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, 5 alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxy carbonyl, alkylaminoacarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including 10 alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "heteroatom" includes atoms of any element other than carbon or 15 hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

The term "heterocycle" or "heterocyclic" includes saturated, unsaturated, aromatic ("heteroaryls" or "heteroaromatic") and polycyclic rings which contain one or more heteroatoms. Examples of heterocycles include, for example, benzodioxazole, benzofuran, benzoimidazole, benzothiazole, benzothiophene, benzoxazole, deazapurine, 20 furan, indole, indolizine, imidazole, isooxazole, isoquinoline, isothiazole, methylenedioxypyphenyl, naphridine, oxazole, purine, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinoline, tetrazole, thiazole, thiophene, and triazole. Other heterocycles include morpholine, piprazine, piperidine, thiomorpholine, and thioazolidine. The heterocycles may be substituted or unsubstituted. Examples of 25 substituents include, for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxy carbonyl, alkylaminoacarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino 30 (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl,

sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkyl, alkylaryl, or an aromatic or heteroaromatic moiety.

It will be noted that the structure of some of the compounds of this invention includes asymmetric carbon atoms. It is to be understood accordingly that the isomers arising from such asymmetry (e.g., all enantiomers and diastereomers) are included within the scope of this invention, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis. Furthermore, the structures and other compounds and moieties discussed in this application also include all tautomers thereof.

10 In a further embodiment, the compound is an antagonist of the MC4-R. In another embodiment, the compound is an agonist of the MC4-R. Compounds which are agonists of MC4-R can be identified using the cAMP assay given in Example 5.

The term "administering" includes routes of administration which allow the MC4-R binding compound to perform its intended function, e.g. interacting with MC4-Rs and/or treating a MC4-R associated state. Examples of routes of administration which can be used include parental injection (e.g., subcutaneous, intravenous, and intramuscular), intraperitoneal injection, oral, inhalation, and transdermal. The injection can be bolus injections or can be continuous infusion. Depending on the route of administration, the MC4-R binding compound can be coated with or disposed in a selected material to protect it from natural conditions which may detrimentally effect its ability to perform its intended function. The MC4-R binding compound can be administered alone or with a pharmaceutically acceptable carrier. Further, the MC4-R binding compound can be administered as a mixture of MC4-R binding compounds, which also can be coadministered with a pharmaceutically acceptable carrier. The MC4-R binding compound can be administered prior to the onset of a MC4-R associated state, or after the onset of a MC4-R associated state. The MC4-R binding compound also can be administered as a prodrug which is converted to another form *in vivo*.

In one embodiment of the invention, the invention includes methods of treating an MC4-R associated state by administering the MC4-R binding compound of the invention in combination with art recognized compounds, e.g., therapeutic agents. For example, a patient suffering from cachexia resulting from HIV, may be treated using both the MC4-R binding compounds of the invention in combination with art recognized

-68 -

compounds for treating the cachexia or HIV itself. The term "combination with" includes both simultaneous administration as well as administration of the MC4-R binding compound before the art recognized compound or after the compound. The period between administrations of the MC4-R binding compound and the other agent 5 may be any length of time which allows the compositions to perform their intended function, e.g., the interval may be between few minutes, an hour, more than one hour, etc. In addition, the MC4-R binding compounds may also be administered in combination with other MC4-R binding compounds of the invention.

The invention also features a pharmaceutical composition for the treatment of a 10 MC4-R associated state in a mammal. The pharmaceutical composition includes a pharmaceutically acceptable carrier and an effective amount of an MC4-R binding compound of the formula (I):



wherein B is an anchor moiety, Z is a central moiety, and E is a MC4-R interacting 15 moiety. In other embodiments, the pharmaceutical compositions of the invention include MC4-R binding compounds of formulae II, III, IV, V, VI, VII, VIII, IX, X, and/or XI. Pharmaceutical compositions comprising pharmaceutically acceptable salts of at least one MC4-R binding compound are also included.

The language "effective amount" of the compound is that amount necessary or 20 sufficient to treat or prevent a MC4-R associated state, e.g. prevent the various morphological and somatic symptoms of a MC4-R associated state. The effective amount can vary depending on such factors as the size and weight of the subject, the type of illness, or the particular MC4-R binding compound. For example, the choice of the MC4-R binding compound can affect what constitutes an "effective amount". One 25 skilled artisan would be able to study the aforementioned factors and make the determination regarding the effective amount of the MC4-R binding compound without undue experimentation. An *in vivo* assay as described in Example 4 below or an assay similar thereto (e.g., differing in choice of cell line or type of illness) also can be used to determine an "effective amount" of a MC4-R binding compound. The ordinarily 30 skilled artisan would select an appropriate amount of a MC4-R binding compound for use in the aforementioned *in vivo* assay. Advantageously, the effective amount is

-69-

effective to treat a disorder associated with pigmentation or weight loss, e.g., weight loss is a result of anorexia nervosa, old age, cancer cachexia, or HIV cachexia.

The regimen of administration can affect what constitutes an effective amount.

The MC4-R binding compound can be administered to the subject either prior to or after

5 the onset of a MC4-R associated state. Further, several divided dosages, as well as staggered dosages, can be administered daily or sequentially, or the dose can be continuously infused, or can be a bolus injection. Further, the dosages of the MC4-R binding compound(s) can be proportionally increased or decreased as indicated by the exigencies of the therapeutic or prophylactic situation.

10 The term "treated," "treating" or "treatment" includes the diminishment or alleviation of at least one symptom associated or caused by the state, disorder or disease being treated. For example, treatment can be diminishment of one or several symptoms of a disorder or complete eradication of a disorder.

15 The language "pharmaceutical composition" includes preparations suitable for administration to mammals, e.g., humans. When the compounds of the present invention are administered as pharmaceuticals to mammals, e.g., humans, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

20 The phrase "pharmaceutically acceptable carrier" is art recognized and includes a pharmaceutically acceptable material, composition or vehicle, suitable for administering compounds of the present invention to mammals. The carriers include liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject agent from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, 25 ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene

-70 -

glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

10 Examples of pharmaceutically acceptable antioxidants include: water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, α -tocopherol, and the like; and metal chelating agents, such as citric acid, 15 ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations of the present invention include those suitable for oral, nasal, topical, transdermal, buccal, sublingual, rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be 20 prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 per cent 25 to about 70 per cent, most preferably from about 10 per cent to about 30 per cent.

Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present 30 invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

- Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.
- 10 In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as, for example,
- 15 carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as, for example, cetyl alcohol and glycerol
- 20 monostearate; absorbents, such as kaolin and bentonite clay; lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules
- 25 using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be

-72-

made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be 5 scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized 10 by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain 15 portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds of the invention 20 include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluent commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3- 25 butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert dilutents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, 30 perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and

-73 -

sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by
5 mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

10 Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions,
15 patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes,
20 paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain
25 customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can
30 also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the active compound in a polymer matrix or gel.

-74 -

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with 5 one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

10 Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating 15 materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal 20 agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

25 In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. 30 Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

-75 -

Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable 5 polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given by forms suitable for each administration 10 route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administration is preferred.

The phrases "parenteral administration" and "administered parenterally" as used 15 herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

The phrases "systemic administration," "administered systemically," "peripheral 20 administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

These compounds may be administered to humans and other animals for therapy 25 by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

Regardless of the route of administration selected, the compounds of the present 30 invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

-76 -

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

5 The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular
10 compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the
15 invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic
20 effect. Such an effective dose will generally depend upon the factors described above. Generally, intravenous and subcutaneous doses of the compounds of this invention for a patient, when used for the indicated analgesic effects, will range from about 0.0001 to about 100 mg per kilogram of body weight per day, more preferably from about 0.01 to about 50 mg per kg per day, and still more preferably from about 1.0 to about 100 mg
25 per kg per day. An effective amount is that amount treats an MC4-R associated state.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

While it is possible for a compound of the present invention to be administered
30 alone, it is preferable to administer the compound as a pharmaceutical composition.

As set out above, certain embodiments of the present compounds can contain a basic functional group, such as amino or alkylamino, and are, thus, capable of forming

-77 -

pharmaceutically acceptable salts with pharmaceutically acceptable acids. The term "pharmaceutically acceptable salts" is art recognized and includes relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds 5 of the invention, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, 10 naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, e.g., Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19).

In other cases, the compounds of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances includes relatively non-toxic, inorganic and organic base 15 addition salts of compounds of the present invention. These salts can likewise be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary 20 or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine 25 and the like.

The term "pharmaceutically acceptable esters" refers to the relatively non-toxic, esterified products of the compounds of the present invention. These esters can be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form or hydroxyl with a 30 suitable esterifying agent. Carboxylic acids can be converted into esters *via* treatment with an alcohol in the presence of a catalyst. Hydroxyls can be converted into esters *via* treatment with an esterifying agent such as alkanoyl halides. The term also includes

-78 -

lower hydrocarbon groups capable of being solvated under physiological conditions, e.g., alkyl esters, methyl, ethyl and propyl esters. (See, for example, Berge et al., *supra*.) A preferred ester group is an acetomethoxy ester group. Preferably, the amount of the MC4-R binding compound is effective to treat a pigmentation or weight loss disorder, e.g., weight loss associated with anorexia nervosa, old age, cachexia, HIV or cancer.

The invention also pertains to packaged MC4-R binding compounds. The packaged MC4-R binding compounds include, an MC4-R binding compound (e.g., of formulae I, II, III, IV, V, VI, VII, VIII, IX, X, and/or XI), a container, and directions for using said MC4-R binding compound to treat an MC4-R associated state, e.g., weight loss, etc.

Examples of MC4-R binding compounds for inclusion in pharmaceutical compositions include, for example,

- 2-[2-(4-benzyloxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 15 2-[2-(2-iodo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-methoxy-5-nitro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(3-chloro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2,5-dimethoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 20 2-[2-(3-bromo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-iodo-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
- 2-[2-(2-methoxy-5-nitro-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
- 2-[2-(2-methoxy-5-nitro-benzyloxy)-phenyl]-1,4,5,6-tetrahydropyrimidine;
- 2-[2-(2-bromo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 25 2-[2-(3-iodo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-methoxy-5-nitro-benzylsulfanyl)-phenyl]-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazole;
- 2-{2-[2-(2-methoxy-naphthalen-1-yl)-ethyl]-phenyl}-1,4,5,6-tetrahydropyrimidine;
- 2-[2-(5-bromo-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine;
- 30 2-{2-[2-(2-methyl-naphthalen-1-yl)-ethyl]-phenyl}-1,4,5,6-tetrahydropyrimidine;
- 2-{2-[2-(2,3-dihydro-benzo[1,4]dioxin-5-yl) -ethyl]-phenyl}-1,4,5,6-tetrahydropyrimidine;

-79 -

- 2-[2-(2-methoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine;
2-(2-Benzylsulfanyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine;
2-(2-Pentadecylsulfanyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine;
2-(2-Cyclohexylmethylsulfanyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine;
5 2-[2-(2-Methyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(3-Nitro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(3,5-Dimethoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(4-Fluoro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Chloro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
10 2-[2-(2-Fluoro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2,4-Bis-trifluoromethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(3-Methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(3,5-Bis-trifluoromethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Methoxy-5-nitro-benzyloxy)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
15 2-[2-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
2-(2-Benzylsulfanyl-phenyl)-4,5-dihydro-1H-imidazole;
2-[2-(2,6-Difluoro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(Naphthalen-1-ylmethoxy)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
20 1-{2-[2-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-5,6-dihydro-4H-pyrimidin-1-yl}-ethanone;
2-[2-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazole;
2-[2-(2-Iodo-benzylsulfanyl)-phenyl]-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazole;
25 2-[2-(2,5-Dimethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
4-[2-(1,4,5,6-Tetrahydro-pyrimidin-2-yl)-phenylsulfanyl]methyl]-quinoline;
2-[2-(2-Methoxy-5-nitro-benzylsulfanyl)-pyridin-3-yl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Cyclopentyloxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
30 2-[2-(2,3-Dihydro-benzo[1,4]dioxin-5-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;

-80 -

- 2-[2-(6-Methoxy-2,3-dihydro-benzo[1,4]dioxin-5-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-fluoro-2-methoxy-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
- 1-Methyl-2-[2-(naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 5 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
- 2-[2-(5-Bromo-2-methoxy-benzyloxy)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(Naphthalen-1-yloxymethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-5,5-dimethyl-1,4,5,6-tetrahydro-pyrimidine;
- 10 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-5,5-dimethyl-4,5-dihydro-1H-imidazole;
- 2-[2-(2,6-Dimethoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Bromo-6-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[5-Bromo-2-(5-bromo-2-methoxy-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
- 15 2-[5-Bromo-2-(5-bromo-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[4-Bromo-2-(5-bromo-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Bromo-5-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 20 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-5-methyl-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(Biphenyl-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Chloro-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Methoxy-5-thiophen-3-yl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
- 25 pyrimidine;
- 2-[2-(Biphenyl-2-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Iodo-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-5-fluoro-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 30 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-1,4,5,6-tetrahydro-pyrimidine;

- 2-[2-(4,4'-Dimethoxy-biphenyl-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(9H-Fluoren-9-ylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(3'-Chloro-4'-fluoro-4-methoxy-biphenyl-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-
- 5 tetrahydro-pyrimidine;
- 2-[2-(1-Naphthalen-1-yl-ethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-5-fluoro-phenyl]-4,5-dihydro-1H-imidazole;
- 2-(2-Benzhydrylsulfanyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2'-Fluoro-4"-methoxy-[1,1';4',1"]terphenyl-3"-ylmethylsulfanyl)-phenyl]-1,4,5,6-
- 10 tetrahydro-pyrimidine;
- 2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzamidine;
- 2-[4-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Ethynyl-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-1,4,5,6-tetrahydro-pyrimidine;
- 15 2-[2-(5-Bromo-2-cyclopentyloxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-ethoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-propoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- [2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-diethyl-amine;
- 20 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-piperazine;
- C-{4-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-quinoxalin-2-yl]-morpholin-2-yl}-methylamine;
- 2-[2-(2-Methoxy-5-methyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzyloxymethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 25 [2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-dimethyl-amine;
- 2-[2-(5-Bromo-2-isopropoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Ethoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Propoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 4-Methoxy-3-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenylsulfanylmethyl]-
- 30 benzonitrile;
- 1-{4-Methoxy-3-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenylsulfanylmethyl]-phenyl}-ethanone;

-82 -

- 2-[2-(Naphthalen-1-ylsulfanyl methyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-piperidine;
C-{4-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-morpholin-2-yl}-
methylamine;
- 5 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-pyrrolidin-3-ylamine;
1-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-pyrrolidin-3-ylamine;
3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-1,5,6,7,8,8a-hexahydro-
imidazo[1,5-a]pyridine;
3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-5,6,7,7a-tetrahydro-1H-
10 pyrrolo[1,2-c]imidazole;
2-[2-(Benzo[b]thiophen-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[3-Fluoro-2-(naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-(Naphthalen-1-ylmethylsulfanyl)-3-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenylamine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-phenyl]-1,4,5,6-tetrahydro-
15 pyrimidine;
2-[2-(2-Methoxy-phenylsulfanyl methyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
1-{2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-5,6-dihydro-4H-pyrimidin-1-yl}-
3-methyl-butan-1-one;
1-{2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-5,6-dihydro-4H-pyrimidin-1-yl}-
20 2-phenyl-ethanone;
2-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-pyridin-2-yl]-1,4,5,6-tetrahydro-pyrimidine;
N-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-guanidine;
2-[2-(2-Isopropoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
- 25 2-[2-(2-Cyclopentyloxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
(5-Bromo-2-methoxy-benzyl)-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenyl]-amine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl methyl)-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
- 30 2-[2-(2-Methoxy-naphthalen-1-ylsulfanyl methyl)-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
2-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-pyrazin-2-yl]-1,4,5,6-tetrahydro-pyrimidine;

-83 -

- 2-[3-Chloro-2-(naphthalen-1-ylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(6-Bromo-2-methoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[3-Chloro-2-(2-methoxy-naphthalen-1-ylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-
5 pyrimidine;
2-[2-(5-Bromo-2-methoxy-phenylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(5-Bromo-2-methoxy-phenylsulfanylmethyl)-3-chloro-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
10 2-[1-(2-Naphthalen-1-yl-ethyl)-1H-pyrrol-2-yl]-1,4,5,6-tetrahydro-pyrimidine;
(5-Bromo-2-methoxy-benzyl)-methyl-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenyl]-
amine;
2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzylamine;
2-[2-(2-Chloro-phenylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
15 2-[2-(2-Bromo-phenylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-(2-o-Tolylsulfanylmethyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2,5-Dichloro-phenylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-(3-Amino-propylamino)-6-(5-bromo-2-methoxy-benzylsulfanyl)-benzonitrile;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-1,4,5,6-tetrahydro-pyrimidine;
20 [2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-diethyl-amine;
4-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-morpholine;
3'-(5-Bromo-2-methoxy-benzylsulfanyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl;
2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-piperazin-1-yl-6,7-dihydro-quinoxaline;
1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-piperidine;
25 C-{4-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-morpholin-2-yl}-
methylamine;
1-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-pyrazin-2-yl]-pyrrolidin-3-ylamine;
1-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-quinoxalin-2-yl]-pyrrolidin-3-ylamine;
1-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-pyrrolidin-3-ylamine;
30 C-{4-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-pyrazin-2-yl]-morpholin-3-yl}-
methylamine;
1-[3-Fluoro-2-(2-naphthalen-1-yl-ethyl)-benzyl]-piperazine;

- 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-azetidine;
1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-pyrrolidin-3-ol;
[2-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester;
- 5 [2-(2-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester;
[2-(2-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 2-piperidin-1-yl-ethyl ester;
{1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-pyrrolidin-2-yl}-
- 10 methanol;
4-tert-Butyl-N-naphthalen-1-ylmethyl-N-(2-piperidin-1-yl-ethyl)-benzamide;
N,N-Dimethyl-N'-naphthalen-2-ylmethyl-N'-naphthalen-1-ylmethyl-propane-1,3-diamine;
N-(5-Bromo-2-methoxy-benzyl)-N',N'-dimethyl-N-naphthalen-1-ylmethyl-propane-1,3-
- 15 diamine;
1-Naphthalen-1-ylmethyl-3-phenethyl-1-(2-piperidin-1-yl-ethyl)-thiourea;
3-(4-Dimethylamino-phenyl)-1-(3-dimethylamino-propyl)-1-naphthalen-1-ylmethyl-thiourea;
4-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzylamino]-piperidine-1-
- 20 carboxylic acid ethyl ester;
2-[2-(2-Naphthalen-1-yl-ethyl)-phenyl]-ethylamine;
Naphthalene-2-sulfonic acid (2-dimethylamino-ethyl)-naphthalen-1-ylmethyl-amide;
1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-2-methoxymethyl-
- 25 pyrrolidine;
(2-Hexyloxy-phenyl)-carbamic acid 2-piperidin-1-yl-1-piperidin-1-ylmethyl-ethyl ester;
3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyloxy]-pyrrolidine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyloxymethyl]-pyrrolidine;
2-[2-(Naphthalen-1-ylsulfanylmethyl)-phenyl]-piperidine;
- 30 3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzylamino]-propan-1-ol;
3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzylamino]-3-methyl-butan-1-ol;
1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-pyrrolidin-3-ol;
{1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-pyrrolidin-2-yl}-methanol;

-85 -

- {1-[2-(Naphthalen-1-ylsulfanyl-methyl)-benzyl]-piperidin-2-yl}-methanol;
2-[2-(Naphthalen-1-ylsulfanyl-methyl)-pyrrolidin-1-yl]-ethyl-N-pyrrolidine;
N-pyrrolyl-[1-(2-naphthalen-1-yl-ethyl)-pyrrolidin-2-ylmethyl]-amine;
1-(2-Naphthalen-1-yl-ethyl)-piperidine-2-carboxylic acid methyl ester;
5 (3-Bromo-benzyl)-(1-ethyl-pyrrolidin-2-ylmethyl)-naphthalen-1-ylmethyl-amine;
3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyloxy]-piperidine;
(5-Bromo-2-methoxy-benzyl)-(1-ethyl-pyrrolidin-2-ylmethyl)-naphthalen-1-ylmethyl-
amine;
(1-Ethyl-pyrrolidin-2-ylmethyl)-naphthalen-2-ylmethyl-naphthalen-1-ylmethyl-amine;
10 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyloxymethyl]-pyrrolidine;
(3-Bromo-benzyl)-(3-imidazol-1-yl-propyl)-naphthalen-1-ylmethyl-amine;
(3-Imidazol-1-yl-propyl)-naphthalen-2-ylmethyl-naphthalen-1-ylmethyl-amine;
[2-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 2-piperidin-1-yl-1-piperidin-
1-ylmethyl-ethyl ester;
15 [2-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 2-dimethylamino-ethyl ester;
1-[2-(Naphthalen-1-ylsulfanyl-methyl)-benzyl]-piperazine;
[3-(2-Methyl-piperidin-1-yl)-propyl]-[2-(naphthalen-1-ylsulfanyl-methyl)-benzyl]-
amine;
1-[3-Chloro-2-(naphthalen-1-ylsulfanyl-methyl)-benzyl]-piperazine;
20 N,N-Dimethyl-N'-(2-naphthalen-1-yl-ethyl)-N'-naphthalen-1-ylmethyl-ethane-1,2-
diamine;
{1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-piperidin-2-yl}-methanol;
1-[2-(2-Naphthalen-1-yl-ethyl)-benzyl]-piperazine;
[3-(2-Methyl-piperidin-1-yl)-propyl]-[2-(2-naphthalen-1-yl-ethyl)-benzyl]-amine;
25 1-[3-Fluoro-2-(2-naphthalen-1-yl-ethyl)-benzyl]-piperazine;
{1-[3-Chloro-2-(naphthalen-1-ylsulfanyl-methyl)-benzyl]-piperidin-2-yl}-methanol;
{1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-piperidin-2-yl}-methanol;
{1-[2-(2-Naphthalen-1-yl-ethyl)-benzyl]-piperidin-2-yl}-methanol;
[3-(2-Methyl-piperidin-1-yl)-propyl]-[2-(2-naphthalen-1-yl-ethyl)-benzyl]-amine;
30 1-[2-(2-Naphthalen-1-yl-ethyl)-benzyl]-pyrrolidin-3-ylamine;
1-Phenyl-3-piperazin-1-yl-5,6,7,8-tetrahydro-isoquinoline-4-carbonitrile;

-86 -

- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-6-ethyl-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(4-Methoxy-biphenyl-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Methoxy-5-phenylethynyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
- 5 pyrimidine;
- 2-[2-(2-Naphthalen-1-yl-ethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[3-(2-Methoxy-naphthalen-1-ylsulfanylmethyl)-thiophen-2-yl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2,5-Dimethoxy-phenylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 10 2-[2-(4-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-4,4-dimethyl-4,5-dihydro-1H-imidazole;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-5,5-dimethyl-1,4,5,6-tetrahydro-pyrimidine;
- 15 2-[3-(Naphthalen-1-ylsulfanylmethyl)-thiophen-2-yl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-phenyl}-1,4,5,6-tetrahydro-pyrimidine;
- 2-[3-Chloro-2-(2-naphthalen-1-yl-ethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-3-fluoro-phenyl}-1,4,5,6-tetrahydro-pyrimidine;
- 20 2-[2-(5-Bromo-2-methoxy-phenylsulfanylmethyl)-3-fluoro-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(Naphthalen-1-ylsulfanylmethyl)-phenyl]-4,5-dihydro-1H-imidazole;
- 2-[3-Fluoro-2-(naphthalen-1-ylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[3-Bromo-2-(naphthalen-1-ylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 25 2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-3-chloro-phenyl}-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Methoxy-5-trifluoromethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[4-(Naphthalen-1-ylsulfanylmethyl)-thiophen-3-yl]-1,4,5,6-tetrahydro-pyrimidine;
- 30 2-[2-(Naphthalen-1-ylsulfanylmethyl)-thiophen-3-yl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-3-trifluoromethyl-phenyl}-1,4,5,6-tetrahydro-pyrimidine;

- 2-[2-(2-Naphthalen-1-yl-ethyl)-3-trifluoromethyl-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(6-Fluoro-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- {1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-piperidin-2-yl}-methanol;
- 2-[3-Fluoro-2-(2-naphthalen-1-yl-ethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 5 [2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-[3-(2-methyl-piperidin-1-yl)-propyl]-amine;
- 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-pyrrolidin-3-ylamine;
- 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-piperazine;
- 5,5-Dimethyl-2-[2-(2-naphthalen-1-yl-ethyl)-phenyl]-4,5-dihydro-1H-imidazole;
- 10 2-[3-Fluoro-2-(2-naphthalen-1-yl-ethyl)-phenyl]-5,5-dimethyl-4,5-dihydro-1H-imidazole;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3,5-difluoro-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3,5-difluoro-phenyl]-5,5-dimethyl-4,5-dihydro-1H-
- 15 dihydro-1H-imidazole;
- 3-(2-Naphthalen-1-yl-ethyl)-2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenylamine;
- Amino-[2-(2-naphthalen-1-yl-ethyl)-phenyl]-acetonitrile;
- 1-[2-(2-Naphthalen-1-yl-ethyl)-phenyl]-ethane-1,2-diamine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-4-methyl-4,5-dihydro-1H-
- 20 imidazole;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-4-methyl-4,5-dihydro-1H-imidazole;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-phenyl]-4-methyl-4,5-dihydro-1H-imidazole;
- 25 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3,4-difluoro-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[3-Fluoro-2-(naphthalen-1-ylsulfanylmethyl)-phenyl]-5,5-dimethyl-4,5-dihydro-1H-imidazole;
- 2-{2-[2-(5-Bromo-2-methoxy-phenyl)-1-methyl-ethyl]-phenyl}-1,4,5,6-tetrahydro-
- 30 pyrimidine;
- 2-[2-(5-Bromo-2-methoxy benzyl sulfanyl)-3-fluoro-4-trifluoromethyl-phenyl]-4,4-dimethyl-4,5-dihydro-1H-imidazole;

-88 -

- 2-[2-(5-Bromo-2-methoxy-benzyl sulfanyl)-3-fluoro-4-trifluoromethyl-phenyl]-5,5-dimethyl-1,4,5,6-tetrahydro-pyrimidine;
- 2-[3-Methoxy-2-(2-naphthalen-1-yl-ethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-phenyl]-1,4,5,6-tetrahydro-
- 5 pyrimidin-5-ol;
- 2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-3-methoxy-phenyl}-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-6-ethyl-1,4,5,6-tetrahydro-pyrimidine, and pharmaceutically acceptable salts thereof. Also included are
- 10 compositions containing the compounds listed in Table 4.

In a further embodiment, the pharmaceutical compositions of the invention include compositions wherein the MC4-R binding compound is not 5-(4-chloro-phenyl)-2,5-dihydro-3H-imidazo[2,1-a]-isoindol-5-ol (MASPINOL; Compound DT).

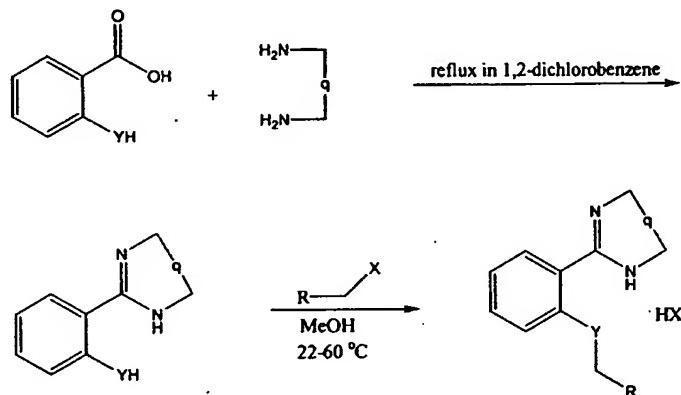
- In another embodiment, the pharmaceutical compositions of the invention include compositions wherein the MC4-R binding compound is not 2-naphthalen-1-ylmethyl-4,5-dihydro-1H-imidazole (NAPHAZOLINE; Compound AS); 10-[2-(1-methyl-piperadin-2-yl)-ethyl]-2-methylsulfanyl-10H-phenothiazine (THORADIAZINE; THIODIAZINE; Compound AP); (2,6-dichloro-phenyl)-imidazolidin-2-ylidene-amine (CLONIDINE; Compound AY); or 2-benzyl-4,5-dihydro-1H-imidazole
- 15 (TOLAZOLINE; Compound AZ).

- In another further embodiment, the pharmaceutical compositions of the invention includes compositions wherein the MC4-R binding compound is not 2-[2-(2,5-dichlorothiophen-3-ylmethylsulfanyl)-phenyl]-1, 4, 5, 6- tetrahydropyrimidine (Compound A); 2[2-(2-chloro- 6-fluoro-benzylsulfanyl)-phenyl]-1, 4, 5, 6-tetrahydropyrimidine (Compound B); 1-(6-bromo-2-chloro-quinolin-4-yl)-3-(2-diethylaminoethyl)-urea (Compound AN); 2-[2-(2,6-difluorobenzylsulfanyl)-phenyl]-1, 4, 5, 6-tetrahydropyrimidine (Compound AO); 1-(4-hydroxy-1, 3, 5-trimethyl-piperadin-4-yl)-ethanone (Compound AR); 4,6-dimethyl-2-piperazin-1-yl-pyrimidine (Compound FP); 2-piperazin-1-yl-pyrimidine (Compound FR); 1-pyridin-2-yl-piperazine
- 25 (Compound FS); 2-piperazin-1-yl-4-trifluoromethyl pyrimidine (Compound FT); 6-piperazin-1-yl-7-trifluoromethyl-thieno[3,2-b]pyridine-3-carboxylic acid methyl ester (Compound FU); 5-bromo-2-piperazin-1-yl)-pyrimidine (Compound FV); 1-(3-
- 30

-89 -

trifluoromethyl-pyridin-2-yl)-piperazine (Compound FW); 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine (Compound FX); piperazine (Compound KY); or (2-Hexyloxy-phenyl)-carbamic acid 2-piperidin-1-yl-1-piperidin-1-ylmethyl-ethyl ester (Compound OQ).

- 5 The compounds of the present invention can be synthesized using standard methods of chemical synthesis and/or can be synthesized using schemes described herein. Synthesis of specific compounds is discussed in detail in the Example sections below. Examples of syntheses of several classes of compounds of the invention are outlined in the schemes below. Scheme 1 depicts a method of synthesizing
 10 thiomethylene compound of the invention.



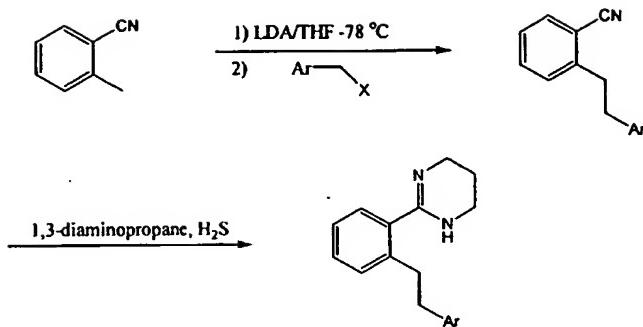
Y = O or S;
 q = bond, CH₂, fused-cyclohexane.
 R = various alkyl, cycloalkyl, aryl or heteroaryl
 X = I, Br or Cl

Scheme 1

- 2-hydroxy or 2-mercaptop benzoic acid is heated with the diamine in refluxing 1,2-dichlorobenzene to form the corresponding heterocyclic compound. The desired
 15 thioether or ether is formed by treating the thiol or alcohol with a corresponding halogenated compound.

Scheme 2 depicts a general preparation of ethanyl-linked compounds of the invention.

-90-

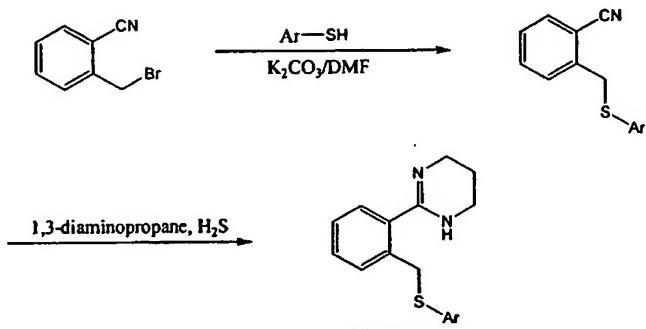


Scheme 2

Scheme 2 shows a method of synthesizing ethanyl linked compounds by treating α -tolunitrile with a lithium base in THF at -78°C . A halogenated alkylaryl compound is then added to form the ethanyl linkage. To form the heterocycle, hydrogen sulfide gas is bubbled through a solution of the nitrile and 1,3 diaminopropane. After formation, the product can then be obtained and purified using standard techniques.

Scheme 3 depicts a method of preparing methylenethio linked compounds of the invention.

10



Scheme 3

As depicted in Scheme 3, the methylenethio compounds of the invention can be prepared by adding anhydrous K_2CO_3 to a thiophenol compound (Ar-SH) in DMF. The solution is then stirred and bromomethyl-benzonitrile is subsequently added. The 15 thioether is then converted to the heterocyclic compound by bubbling hydrogen sulfide through a solution of the thioether and 1,3 diaminopropane. After formation, the product can then be obtained and purified using standard techniques.

-91 -

The invention is further illustrated by the following examples which in no way should be construed as being further limiting. The contents of all references, pending patent applications and published patent applications, cited throughout this application are hereby incorporated by reference. It should be understood that the animal models used throughout the examples are accepted animal models and that the demonstration of efficacy in these animal models is predictive of efficacy in humans.

EXEMPLIFICATION OF THE INVENTION:

10 **EXAMPLE 1: Synthesis of Compounds B, HO, and IZ**

Synthesis of Compound B

2-(4,5-Dihydro-1H-imidazol-2-yl)-benzenethiol. To a suspension of 20.0 g (0.112 mol) of thiosalicylic acid in 200 mL of 1,2-dichlorobenzene was added 21.6 mL (0.323 mol) of ethylenediamine. The mixture was refluxed under nitrogen for 4 h then cooled to ca. 60 °C and 50 mL of methanol was added. The solution was allowed to stand at 22 °C over night and the resulting yellow crystalline solid collected and washed with ether to give 10.6 g of pure product.

2-[2-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
20 hydrochloride (Compound B). To a solution of 750 mg (3.90 mmol) of 2-(1,4,5,6-Tetrahydro-pyrimidin-2-yl)-benzenethiol was added 1.04 g (5.81 mmol) of 1-Chloro-2-chloromethyl-3-fluoro-benzene. The solution was stirred overnight at 22 °C and 2-3 mL of ether was added to induce crystallization. The crystals were collected and washed with ether to give 1.34 g of product.

25 **NMR Data for Compound B**

¹H NMR (300 MHz, CD₃OD) δ 2.01-2.09 (2H, m), 3.49 (4H, br t, J = 5.8 Hz), 4.28 (2H, s), 7.01-7.07 (1H, m), 7.22-7.33 (2H, m), 7.48 (2H, m), 7.56-7.64 (1H, m), 7.75 (1H, d, J = 7.8 Hz)

30

Synthesis of Compound HO:

-92-



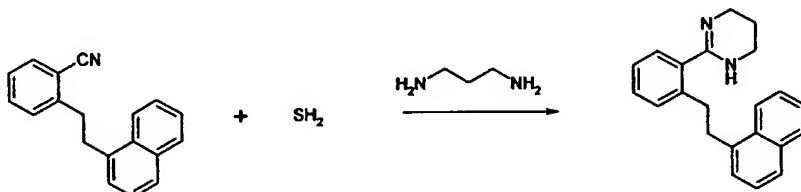
Compound HO



Scheme 4

5

2-(2-Naphthalen-1-yl-ethyl)-benzonitrile. A solution of 1.26 mL (911 mg, 9.00 mmol) of diisopropylamine in 50 mL of THF (tetrahydrofuran) was cooled to -78 °C under nitrogen and 5.6 mL (9.0 mmol) of *n*-butyllithium, 1.6 M in hexanes, was added via syringe. The mixture was stirred at -78 °C for 1 hour and a solution of 353 mg (3.00 mmol) of α-tolunitrile in 10 mL of THF was added. The solution was stirred at -78 °C for one additional hour and a solution of 1.57 mL (9.00 mmol) of HMPA and 583 mg (3.30 mmol) of 1-chloromethylnaphthalene in 10 mL of THF was added dropwise. After stirring for one additional hour at -78°C, the reaction was quenched with water and extracted with Et₂O (diethyl ether) (2x30 mL). The organic layer was washed with aqueous 1 N HCl (30mL), water (3x30mL), brine (30mL) and dried (Na₂SO₄). The solvent was evaporated to give 735 mg of crude product which was used directly in the next step.



Scheme 5

20 2-[2-(2-Naphthalen-1-yl-ethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine (Compound IQ). Hydrogen sulfide gas was bubbled through a solution of 735 mg of crude 2-(2-Naphthalen-1-yl-ethyl)-benzonitrile in 5 mL of 1,3-diaminopropane for 5 minutes, as

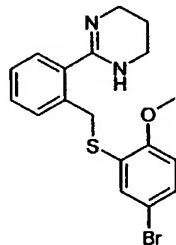
-93 -

depicted in Scheme 3. The reaction was capped and heated to 80 °C for 72 hours. The reaction mixture was then diluted with 5 mL of water and extracted with ethyl acetate (2x10mL). The organic extracts were washed with water (3x10mL), brine (2x10mL), dried (Na_2SO_4) and the solvent was evaporated. The residue was purified on silica gel 5 (eluting with 90:10:1:1 of dichloromethane/methanol/water/formic acid) to afford 310 mg of the formate salt of the product as a colorless oil.

NMR Data for Compound HO:

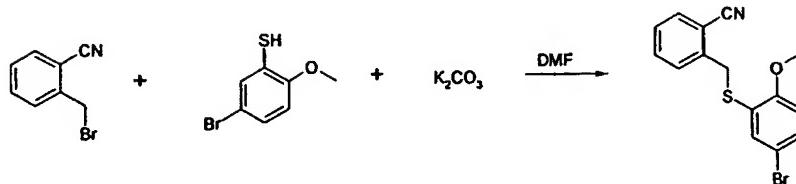
^1H NMR (300 MHz, CDCl_3) δ 1.35-1.50 (2H, m), 2.80-2.95 (4H, m), 3.03 (2H, t, J = 6.8), 3.30 (2H, t, J = 6.8), 6.77 (1H, d, J = 6.9), 7.03-7.30 (3H, m), 7.30-7.57 (4H, m), 7.67 (1H, d, J = 8.1), 7.80-7.90 (1H, m), 7.94-8.03 (1H, m), 8.06 (2H, brs, formate salt).

Synthesis of Compound IZ:



15

Compound IZ

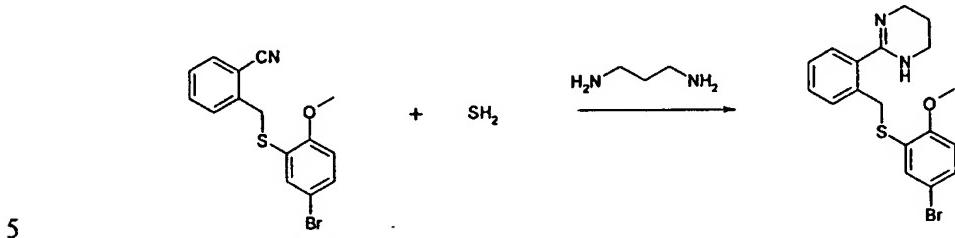


Scheme 6

2-(5-Bromo-2-methoxy-phenylsulfanyl)methyl-benzonitrile. As depicted in Scheme 4 above, to a solution of 104 mg (0.470 mmol) of 2-methoxy-5-bromo-thiophenol in 5 mL 20 of DMF was added 162 mg (1.18 mmol) of anhydrous to a solution of 104 mg (0.470 mmol) of 2-methoxy-5-bromo-thiophenol in 5 mL of DMF was added 162 mg (1.18 mmol) of anhydrous K_2CO_3 . The solution was stirred for 15 minutes at 22 °C and 103 mg (0.520 mmol) of 2-bromomethyl-benzonitrile was added. The reaction was capped and heated to 40 °C for 12 hours. The mixture was subsequently diluted with 5 mL of

-94 -

water and extracted with ethyl acetate (2x10mL). The organic extracts were washed with water (3x10mL), brine (2x10mL), and dried (Na_2SO_4). The solvent was evaporated and the product was purified on silica gel (eluting with 9:1 of hexane/ethyl acetate) to afford 102 mg of the product as a colorless oil.



Scheme 7

2-[2-(5-Bromo-2-methoxy-phenylsulfanyl)methyl]-1,4,5,6-tetrahydro-pyrimidine. (Compound DV) Compound DV was obtained from 2-(5-Bromo-2-methoxy-phenylsulfanyl)methylbenzonitrile, 1,3-propanediamine and hydrogen sulfide in 73% yield by a procedure analogous to that used for the preparation of 2-[2-(2-Naphthalen-1-yl-ethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine described above. Following chromatography, the material was converted to the hydrochloride salt and recrystallized from methanol/ether.

15 NMR Data for Compound IZ

^1H NMR (300 MHz, DMSO- d_6) δ 1.95-2.10 (2H, m), 3.45-3.55 (4H, m), 3.86 (3H, s), 4.40 (2H, s), 6.97-7.04 (1H, m), 7.36-7.65 (6H, m), 10.03 (2H, s, hydrochloride salt).

The compounds given in Table 1, were made using procedures similar to that
20 used for Compound B. The ES-LRMS values each had a relative intensity of 100.

-95 -

Table 1: Physical Data of Selected MC4-R Binding Compounds

ID	Name	Molecular Formula	Exact Mass (free Base)	ES- LRMS found (M+H)	Melt Point (°C)
I	2-[2-(4-Benzyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine; hydrochloride	C ₂₄ H ₂₄ N ₂ OS HCl	388.16	389.6	178- 179
M	2-[2-(2-Iodo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; hydrochloride	C ₁₇ H ₁₇ IN ₂ S HCl	408.02	409	207- 209
N	2-[2-(2-Methoxy-5-nitro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; hydrobromide	C ₁₈ H ₁₉ N ₃ O ₃ S HBr	357.11	358.1	239- 241
O	2-[2-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; hydrochloride	C ₂₁ H ₂₀ N ₂ S HCl	332.13	333.1	207- 208
Q	2-[2-(3-Chloro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; hydrobromide	C ₁₇ H ₁₇ ClN ₂ S HBr	316.08	317	224- 225.5
AI	2-[2-(2,5-Dimethoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; hydrochloride	C ₁₉ H ₂₂ N ₂ O ₂ S HCl	342.14	343.2	201- 202
Z	2-[2-(3-Bromo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; hydrobromide	C ₁₇ H ₁₇ BrN ₂ S HBr	360.03	361	210- 211
B	2-[2-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; hydrochloride	C ₁₇ H ₁₆ ClFN ₂ S HCl	334.07	335	232- 233
AE	2-[2-(2-Iodo-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole; hydrochloride	C ₁₆ H ₁₅ IN ₂ S HCl	394	394.9	184- 185
AF	2-[2-(2-Methoxy-5-nitro-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole; hydrobromide	C ₁₇ H ₁₇ N ₃ O ₃ HBr	343.1	344.1	253- 254
Y	2-[2-(2-Methoxy-5-nitro-benzyloxy)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; hydrochloride	C ₁₈ H ₁₉ N ₃ O ₄ HCl	341.14	342.1	220- 221
AA	2-[2-(2-Bromo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; hydrobromide	C ₁₇ H ₁₇ BrN ₂ S HBr	360.03	361.0 (rel. int.= 96)	177- 179
P	2-[2-(3-Iodo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; hydrobromide	C ₁₇ H ₁₇ IN ₂ S HBr	408.02	409	183- 185
AG	2-[2-(2-Methoxy-5-nitro-benzylsulfanyl)-phenyl]-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazole; hydrobromide	C ₂₁ H ₂₂ N ₂ O ₃ S HBr	397.15	398.1	>240
AL	2-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; hydrochloride	C ₂₂ H ₂₂ N ₂ OS HCl	362.1	363	
AM	2-[2-(5-bromo-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; hydrochloride	C ₁₈ H ₁₉ BrN ₂ OS HCl	390	390.9	

-96-

Example 2: Scincillation Proximity Assay (SPA)

High-Throughput Receptor Binding Screening for MC4-R Binding Compounds

A. Preparation of Membranes from MC4-R Cells

5 A crude preparation of plasma membranes, of sufficient purity for use in the scincillation proximity assay (SPA), was prepared using the following protocol (Maeda et al. (1983) *Biochem. Biophys. Acta* 731:115-120).

MC4-R cells were stable recombinant K293 cells overexpressing the MC4-R. The cells were routinely cultured and passaged in a growth medium composed of

10 DMEM base medium: 10% fetal bovine serum (FBS), 1X Glutamine, and 0.5 mg/ml G418. Terminal cultures (i.e., those which will be processed to produce plasma membranes) were grown in identical media, with the exception that the media contained 0.2 mg/ml G418.

At 4°C, harvested cells were pelleted and immediately washed with 25 mL of

15 PBS. The washed cells were resuspended in two volumes of STM buffer (0.25 M sucrose, 5 mM Tris, 1 mM MgCl₂, pH 7.5), containing Boehringer Complete™ protease inhibitors. Cell breakage was accomplished using a Dounce homogenizer. After 20-30 strokes, nuclei and unbroken cells were pelleted by centrifugation at 1100 rpm for 5 minutes. The supernatant was saved and the pellet was resuspended in 1 volume of

20 STM/protease inhibitors, and then a further lysis step was carried out by the Dounce homogenizer (10-20 strokes). This material was then combined with the first supernatant. 11.25 mL of the homogenate was gently layered on top of 27.25 mL f 42% (w/w) sucrose (5 mM Tris, 1 mM MgCl₂, pH 7.5). After spinning at 28,000 rpm (ultracentrifuge, SW-28 rotor) for 90 minutes, membranes were collected at the interface

25 with a transfer pipette.

The membrane suspension obtained from the sucrose interface was collected and diluted with 5 mM Tris and 1 mM MgCl₂. Membranes were collected by a further round of centrifugation at 33,000 rpm for 30 minutes (SW-41 Ti rotor). The pellet of membranes was subsequently resuspended in a small (0.5 mL) volume of STM, using a

30 2 mL Dounce homogenizer, and immediately frozen. The resulting membranes were stable to both freeze-thaw cycles and temperatures around 4°C for at least 6 hours.

B. High-throughput screen

A scincillation proximity assay (SPA) format ligand binding assay was used. The membranes from the MC4-R mammalian cells (K293 expressing MC4-R) were bound to wheat germ agglutinin (WGA) coated SPA beads. The membrane coated SPA 5 beads were added to screening plates, which contained the test compounds pre-dissolved in 30 μ L of 10% DMSO. After pre-equilibration of the receptor coated beads with the test compounds (1 hour), 2nM of radioactive ligand ($[^{125}\text{I}]$ NDP- α -MSH) was added. Since the binding of the radioactive ligand to the receptor causes the scincillation of the 10 beads, blockage of the binding of the radioactive ligand by a small molecule causes a reduction in scincillation.

1. Pre-Binding of the MC4R Membranes to the WGA-SPA beads

The membranes were mixed with the SPA beads to make a 2X stock of membrane and beads.

15 For a twenty plate batch of screening plates, the components were mixed in proportions given in Table 2. The membranes and beads were stirred with a magnetic stir bar at room temperature for 1-2 hours to allow binding.

Table 2

20

Component	Volume	Final Concentration in Assay
4 mg/ml WGA-SPA Beads	14.4 mL	25 $\mu\text{g}/\text{well}$
MC4R crude plasma membranes	600 μL	5 $\mu\text{g}/\text{well}$
SPA Binding Buffer	100 mL	N/A

the exact amount of membranes used varies with the quality of the membrane preparation and must be checked for each new batch.

2. Binding Assay

The following assay was performed with automation using a Titertec MultiDrop 25 with plate stacker.

30 μL of 10% DMSO was added per well to the dried compound film in an OptiPlate. Then, 5 μL of cold NDP- α -MSH was added to the control wells.

-98 -

Subsequently, 50 μ L per well of 2X membranes and beads were added and pre-equilibrated with the compounds for 1 hour.

Binding was initiated by adding 20 μ L of radioactive ligand (a 20 nM solution of [125 I]-NDP- α -MSH) to each test well. The plates were incubated overnight at room temperature and read the following morning.

The reagents and amounts are summarized below in Table 3.

Table 3

Reagent	Volume (μ L)			
	Max (100%)	Min (0%)	50%	Test
20% DMSO	30	30	30	30
2X membranes + beads	60	0	60	60
2nM [125 I]-NDP- α -MSH in binding buffer	20	20	20	20
NDP- α -MSH (5 μ M in H ₂ O)	5	0	0	0
NDP- α -MSH (20 nM in H ₂ O)	0	0	5	0
Test Compound*	0	0	0	5 μ M

* Test compound stock diluted in BuOH 1:10, 25 μ L dried in assay plate in hood prior to addition of assay buffer. Well contained 0.5 nmol of each test compound (20/well) in 2.5 μ L 100% DMSO.

10

Potency of inhibitors was quantified with respect to positive (100% inhibition) and negative (no inhibitor; 0% inhibition) controls. The following formula was used:

$$\% \text{ Inhibition} = \{1 - [\text{cpm} - (\text{positive control})]/[(\text{negative control}) - (\text{positive control})]\} * 100\%$$

15

Results from the SPA, are summarized in Table 4. In Table 4, * indicates good inhibition of the MC4-R, ** indicates very good inhibition of the MC4-R, and *** indicates exemplary inhibition of the MC4-R.

Compounds which were found to be not active as MC4-R binding compounds, 20 using the SPA assay described herein, are depicted in Table 5.

In an embodiment, the present invention pertains to the compounds and methods described herein provided that the compound is not selected from the group consisting of those depicted in Table 5.

-99-

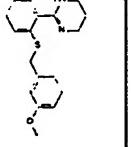
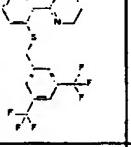
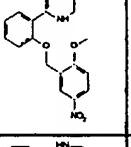
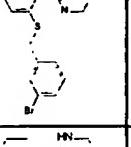
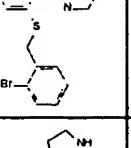
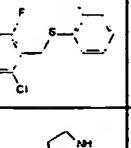
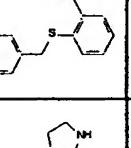
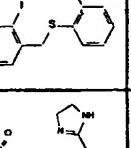
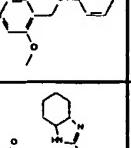
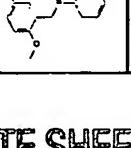
Table 4

ID	CHEMICAL NAME	Mol Weight (Tol)	Structure	MC4-R Binding
A	2-[2-(2,5-Dichlorothiophen-3-ytmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	393.7877		**
B	2-[2-(2-Chloro-6-fluorobenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	415.7566		**
D	2-(2-Benzylsulfanyl-phenyl)-1,4,5,6-tetrahydropyrimidine; HBr	363.3214		*
E	2-(2-Pentadecylsulfanyl-phenyl)-1,4,5,6-tetrahydropyrimidine; HBr	483.6		*
F	2-(2-Cyclohexylmethylsulfanyl-phenyl)-1,4,5,6-tetrahydropyrimidine; HBr	369.369		*
G	2-[2-(2-Methylbenzylsulfanyl-phenyl)-1,4,5,6-tetrahydropyrimidine; HBr	377.3483		*
H	2-[2-(3-Nitrobenzylsulfanyl-phenyl)-1,4,5,6-tetrahydropyrimidine; HBr	408.319		*
I	2-[2-(4-Benzoyloxybenzylsulfanyl-phenyl)-1,4,5,6-tetrahydropyrimidine; HCl	424.9934		**

-100-

M	2-[2-(2-Iodo-benzylsulfonyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	444.7659		**
N	2-[2-(2-Methoxy-5-nitrobenzylsulfonyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	438.3453		***
O	2-[2-(Naphthalen-1-ylmethylsulfonyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	368.9293		***
P	2-[2-(3-Iodo-benzylsulfonyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	489.2179		**
Q	2-[2-(3-Chlorobenzylsulfonyl)-phenyl]-1,4,5,6-tetrahydropyrimidine	397.7662		*
R	2-[2-(3,5-Dimethoxybenzylsulfonyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	378.922		**
S	2-[2-(4-Fluorobenzylsulfonyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	381.3119		*
T	2-[2-(2-Chlorobenzylsulfonyl)-phenyl]-1,4,5,6-tetrahydropyrimidine	397.7662		*
U	2-[2-(2-Fluorobenzylsulfonyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	381.3119		*
V	2-[2-(2,4-Bis(trifluoromethyl)benzylsulfonyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	499.3179		*

-101-

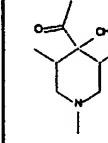
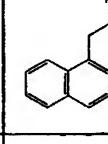
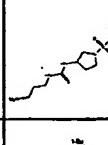
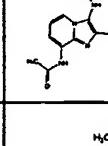
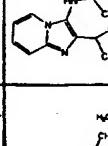
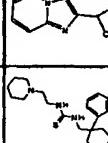
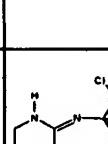
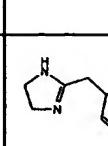
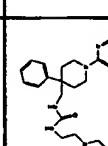
W	2-[2-(3-Methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-Pyrimidine; HCl	348.8957		*
X	2-[2-(3,5-Bis-trifluoromethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-Pyrimidine; HCl	454.8659		*
Y	2-[2-(2-Methoxy-5-nitro-benzyloxy)-phenyl]-1,4,5,6-tetrahydro-Pyrimidine; HCl	377.8267		**
Z	2-[2-(3-Bromo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; HBr	442.2175		**
AA	2-[2-Bromo-benzylsulfanyl]-phenyl]-1,4,5,6-tetrahydropyrimidine	442.2175		**
AB	2-[2-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole	357.2777		*
AC	2-(2-Benzylsulfanyl-phenyl)-4,5-dihydro-1H-imidazole; HCl	304.8425		*
AE	2-[2-(2-Iodo-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole; HCl	430.7391		**
AF	2-[2-(2-Methoxy-5-nitro-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole; HBr	424.3184		**
AG	2-[2-(2-Methoxy-5-nitro-benzylsulfanyl)-phenyl]-3a,4,5,6,7,7a-hexahydro-1H-benzimidazole; HBr	478.41		***

SUBSTITUTE SHEET (RULE26)

-102-

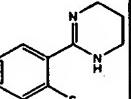
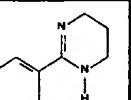
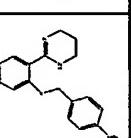
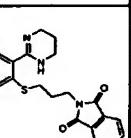
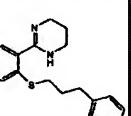
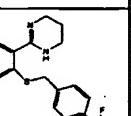
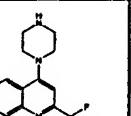
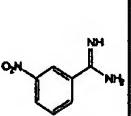
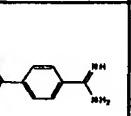
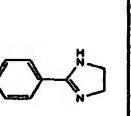
AH	2-[2-(Naphthalen-1-ylmethoxy)-phenyl]-1,4,5,6-tetrahydropyrimidine; Formate	362.4327		**
AI	2-[2-(2,5-Dimethoxybenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	378.922		**
AJ	2-[2-(2-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine	346.4962		***
AK	1-(2-{2-(2-Chloro-6-fluorobenzylsulfanyl)-phenyl}-5,6-dihydro-4H-pyrimidin-1-yl)-ethanone	376.8819		**
AL	2-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	398.9556		***
AM	2-(2-(5-Bromo-2-methoxy-2-benzylsulfanyl)-phenyl)-1,4,5,6-tetrahydropyrimidine; HCl	427.7917		***
AN	1-(8-Bromo-2-chloro-quinolin-4-yl)-3-(2-diethylaminoethyl)-urea	399.7179		*
AO	2-[2-(2,6-Difluorobenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	480.2143		*
AP	10-[2-(1-Methyl-piperidin-2-yl)-ethyl]-2-methylsulfanyl-10H-phenothiazine; HCl	407.0429		*
AQ	4-(3,5-Bis(trifluoromethyl)-phenyl)-1,4,6,7-tetrahydroimidazo[4,5-c]pyridine-5-carbothioic acid (3-diethylamino-propyl)-amide	507.5465		*

- 103 -

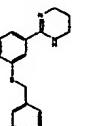
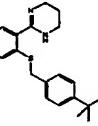
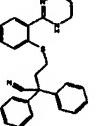
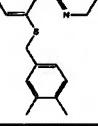
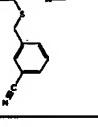
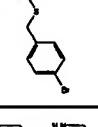
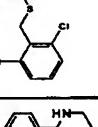
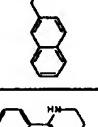
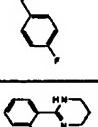
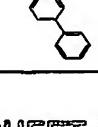
AR	1-(4-Hydroxy-1,3,5-trimethyl-piperidin-4-yl)-ethanone	185.2664		**
AS	2-Naphthalen-1-ylmethyl-4,5-dihydro-1 <i>H</i> -imidazole; HCl	246.7386		*
AT	1-(3-Diethylamino-propyl)-3-[1-[5-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yl)-thiophene-2-sulfonyl]-pyrrolidin-3-yl]-thiourea	552.7096		*
AU	N-[2-Cyclopropyl-3-(1,1,3,3-tetramethylbutylamino)-imidazo[1,2-e]pyridin-8-yl]-acetamide	342.4846		*
AV	(2-Isopropyl-imidazo[1,2-a]pyridin-3-yl)-(1,1,3,3-tetramethyl-butyl) amine	342.4846		*
AW	(2-Isopropyl-imidazo[1,2-a]pyridin-3-yl)-(1,1,3,3-tetramethyl-butyl) amine	287.4485		*
AX	1-(4-Phenyl-5-indolomethyl-3,4,5,6-tetrahydro-2H-1,2-bispyridin-4-phenyl-2-O-phenyl-1-oxoethyl)-benzene	505.6509		*
AY	(2,6-Dichlorophenyl)-imidazolidin-2-ylidene-amine; HCl	266.5561		*
AZ	2-Benzyl-4,5-dihydro-1 <i>H</i> -imidazole	160.2188		*
BA	1-(4-Phenyl-5-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2]bispyridin-4-ylmethyl)-3-(2-piperidin-1-yl-ethyl)-urea	489.5843		*

SUBSTITUTE SHEET (RULE 26)

-104-

BB	2-(2-Methylsulfanyl-phenyl)-1,4,5,6-tetrahydropyrimidine	334.2216		*
BZ	2-(1,4,5,6-Tetrahydropyrimidin-2-yl)-benzenethiol	192.2848		*
BD	2-[2-(4-Nitrobenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine	408.319		*
BE	2-[3-[2-(1,4,5,6-Tetrahydropyrimidin-2-yl)-phenylsulfanyl]propyl]-isoindole-1,3-dione; HBr	460.3948		*
BF	2-[2-(3-Phenylpropylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	391.3752		*
BG	2-[2-(4-Trifluoromethylbenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	431.3197		*
BH	4-Piperazin-1-yl-2-trifluoromethylquinoline	281.2806		*
BI	3-Nitrobenzemidine; HC	201.6116		*
BJ	4-Carbamimidoylbenzamide	163.1791		*
BK	2-Phenyl-4,5-dihydro-1H-imidazole	146.1919		*

-105-

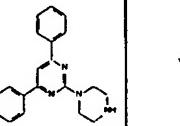
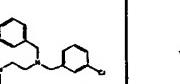
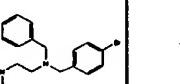
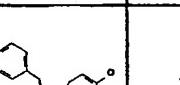
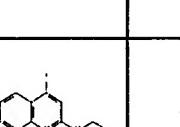
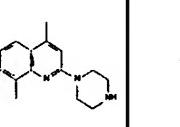
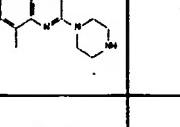
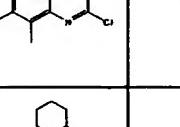
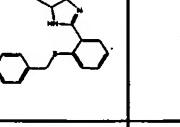
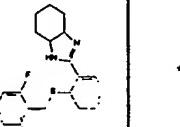
BL	2-(3-Benzylsulfanyl-phenyl)-1,4,5,6-tetrahydropyrimidine	282.4094		*
BM	2-[2-(4-tert-Butylbenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine, HBr	419.4289		*
BN	2,2-Diphenyl-4-[2-(1,4,5,6-tetrahydropyrimidin-2-yl)phenylsulfanyl]butyronitrile, HBr	492.4827		*
BO	2-[2-(3,4-Dimethylbenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine, HCl	346.9232		*
BQ	3-[2-(1,4,5,6-Tetrahydropyrimidin-2-yl)phenylsulfanylmethyl]-benzonitrile, HBr	388.3312		*
BR	2-[2-(4-Bromobenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine, HBr	442.2175		*
BS	2-[2-(2,6-Dichlorobenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine, HBr	432.2109		*
BT	2-[2-(Naphthalen-2-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine, HBr	413.3813		*
BU	2-[2-(4-Fluorobenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine, HBr	381.3119		*
BV	2-[2-(Biphenyl-4-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine, HCl	394.9672		*

-106-

BW	2-[2-(2,4-Bis-trifluoromethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-Pyrimidine; HBr	499.3179		*
BX	2-[2-(1,4,5,6-Tetrahydro-Pyrimidin-2-yl)-phenylsulfanyl]methyl-benzonitrile; HBr	388.3312		*
BY	4-[2-(1,4,5,6-Tetrahydro-pyrimidin-2-yl)-phenylsulfanyl]methyl-benzonitrile; HBr	388.3312		*
BZ	2-[2-(4-Methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-Pyrimidine; HCl	348.8957		*
CA	Benzamidine; HCl	156.614		*
CB	3,5-Bis-trifluoromethyl-benzamidine; HCl	292.6105		*
CC	2-(2-Benzylsulfanyl-phenyl)-4,5-dihydro-1H-imidazole; HCl	304.8425		*
CD	(2-Butoxy-phenyl)-carbamic acid 2-piperdin-1-yl-1-piperidin-1-ylmethyl-ethyl ester; Formate	463.6221		**
CE	(2-Pentyloxy-phenyl)-carbamic acid 2-piperdin-1-yl-1-piperidin-1-ylmethyl-ethyl ester; Formate	477.649		**
CF	2-(2-Bromo-phenyl)-4,5-dihydro-1H-imidazole; HCl	261.5479		*

SUBSTITUTE SHEET (RULE 26)

-107-

CJ	4-Phenyl-2-piperazin-1-yl-6-p-tolyl-pyrimidine	330.4326		*
CK	N-Benzyl-N-(3-chloro-benzyl)-N,N-dimethyl-ethane-1,2-diamine	302.8468		*
CL	N-Benzyl-N-(4-bromo-benzyl)-N,N-dimethyl-ethane-1,2-diamine	347.2981		*
CM	N-Benzyl-N-(3,4-dichloro-benzyl)-N,N-dimethyl-ethane-1,2-diamine	337.2916		*
CO	7-Chloro-4,8-dimethyl-2-piperazin-1-yl-quinoline; Oxalate	365.8208		*
CP	7-Chloro-4,8-dimethyl-2-piperazin-1-yl-quinoline	275.7808		*
CQ	7-Chloro-4,8-dimethyl-2-piperazin-1-yl-quinoline; Formate	321.8108		*
CS	2,7-Dichloro-4,8-dimethyl-quinoline	226.1046		*
CT	2-(2-Benzylsulfanyl-phenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzimidazole; HCl	358.9342		*
CU	2-[2-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-3a,4,5,6,7,7a-hexahydro-1H-benzimidazole; HCl	411.3694		**

SUBSTITUTE SHEET (RULE 26)

-108-

CV	2-[2-(2-Iodo-benzylsulfanyl)-phenyl]-3a,4,5,6,7,7b-hexahydro-1H-benzimidazole; HCl	484.8307		**
CY	1-Phenyl-3-piperazin-1-yl-5,6,7,8-tetrahydro-isouquinoline-4-carbonitrile	318.4216		**
CZ	2-[2-(Pyridin-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine	283.3972		*
DA	1-Pyridin-3-ylmethyl-2-[2-(pyridin-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine	374.5096		*
DB	2-[2-(2-Ethoxyethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	345.3037		*
DC	2-[2-(2,5-Dimethylbenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	346.9232		**
DD	2-[2-(2-Benzenesulfonylmethylbenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	517.5108		*
DE	4-[2-(1,4,5,6-Tetrahydropyrimidin-2-yl)-phenylsulfanyl]methyl-quinoline; HBr	414.3691		**
DF	2-[2-(2-Methoxy-5-nitrobenzylsulfanyl)-pyridin-3-yl]-1,4,5,6-tetrahydropyrimidine; HBr	439.3331		**
DG	2-[2-(2-Methoxybenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	348.8957		**

SUBSTITUTE SHEET (RULE 26)

-109-

DH	2-[2-(2-Cyclopentyloxybenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	447.4393		**
DI	2-Biphenyl-2-yl-1,4,5,6-tetrahydropyrimidine; Formate	282.3465		*
DJ	2-[2-(2,3-Dimethoxybenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	423.374		*
DK	2-[2-(2,3-Dihydrobenzo[1,4]dioxin-5-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	421.3581		**
DL	2-[2-(6-Methoxy-2,3-dihydrobenzo[1,4]dioxin-5-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine	451.3844		***
DM	2-[2-(5-fluoro-2-methoxybenzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole; HCl	411.3381		**
DN	1-Methyl-2-[2-(naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; formate	392.5262		**
DO	1-Methyl-2-[2-(naphthalen-1-ylmethylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole	332.4693		***
DP	2-[2-(5-Bromo-2-methoxybenzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole; HCl	413.7649		***
DQ	2-[2-(5-Bromo-2-methoxybenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	411.7251		***

SUBSTITUTE SHEET (RULE 26)

-110-

DR	2-[2-(Naphthalen-1-yloxymethyl)-phenyl]-1,4,5,6-tetrahydropyrimidine	316.4027		**
DS	2-(2-Phenoxy-phenyl)-1,4,5,6-tetrahydropyrimidine; HCl	288.7759		*
DT	5-(4-Chlorophenyl)-2,5-dihydro-3H-imidazo[2,1-e]isoindol-5-ol	284.7448		*
DU	2-[2-(2-Methoxy-phenoxy-methyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	332.8291		*
DV	2-[2-(2,6-Dimethoxy-phenoxy-methyl)-phenyl]-1,4,5,6-tetrahydropyrimidine	326.3954		*
DW	2-[2-(5-Bromo-2-methoxybenzylsulfanyl)-phenyl]-5,5-dimethyl-1,4,5,6-tetrahydropyrimidine	419.3855		***
DX	2-[2-(2-Methoxy-phenoxy)-phenyl]-1,4,5,6-tetrahydropyrimidine; Formate	328.3722		*
DY	2-[2-(5-Bromo-2-methoxybenzylsulfanyl)-phenyl]-5,5-dimethyl-4,5-dihydro-1H-imidazole	405.3586		***
DZ	2-[2-(5-Bromo-2-methoxybenzylsulfanyl)-5-trifluoromethyl-phenyl]-1,4,5,6-tetrahydropyrimidine	459.33		*
EA	2-[2-(2,6-Dimethoxybenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	378.922		***

SUBSTITUTE SHEET (RULE26)

-111-

EB	2-[2-(5-Bromo-2-methoxybenzylsulfonyl)-phenyl]-6-ethyl-1,4,5,6-tetrahydropyrimidine	419.3855		***
EC	2-(5-Bromo-2-methoxybenzylsulfonyl)-benzonitrile	334.2364		*
ED	2-[2-(2-Bromo-6-methoxybenzylsulfonyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	472.2437		***
EF	2-[5-Bromo-2-(5-bromo-2-methoxybenzylsulfonyl)-phenyl]-4,5-dihydro-1H-imidazole; Formate	502.2309		***
EJ	9-Benzylidene-1,2,3,9-tetrahydro-4,9a-diazafluorene; Formate	306.3685		*
EK	2-[2-(Biphenyl-3-yloxy-phenyl)-4,5-dihydro-1H-imidazole	314.3868		*
EL	2-[2-(4-Chlorophenoxy)-phenyl]-4,5-dihydro-1H-imidazole	272.7338		*
EM	2-[5-Bromo-2-(5-bromo-2-methoxybenzylsulfonyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; Formate	516.2578		***
EN	2-[2-(Naphthalen-2-yloxy)-phenyl]-4,5-dihydro-1H-imidazole; Formate	334.3789		*
EO	2-[4-Bromo-2-(5-bromo-2-methoxybenzylsulfonyl)-phenyl]-1,4,5,6-tetrahydropyrimidine	470.2278		**

-112-

EP	2-[2-(2-Bromo-5-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	472.2437		***
EQ	2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-5-methyl-phenyl]-1,4,5,6-tetrahydropyrimidine	405.3586		***
ER	2-[2-(Naphthalen-1-yloxy)-phenyl]-4,5-dihydro-1H-imidazole; formate	334.3789		*
ES	2-[2-(Naphthalen-1-yloxy)-phenyl]-1,4,5,6-tetrahydropyrimidine; Formate	348.4058		*
ET	2-[2-(Biphenyl-3-ymethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	439.4192		**
EU	2-[2-(Naphthalen-2-yloxy)-phenyl]-1,4,5,6-tetrahydropyrimidine; Formate	348.4058		*
EV	2-[2-(5-Bromo-2-methoxy-phenylmethanesulfonyl)-phenyl]-1,4,5,6-tetrahydropyrimidine	407.3311		*
EW	2-[2-(5-Chloro-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	383.3404		***
EX	2-[2-(2-Methoxy-5-thiophen-3-yl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	431.0216		***
EY	2-[2-(Biphenyl-2-ymethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; Formate	404.5372		**

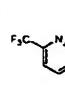
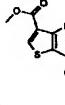
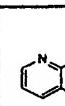
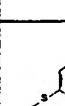
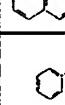
-113-

EZ	2-[2-(5-Iodo-2-methoxybenzylsulfanyl)phenyl]-1,4,5,6-tetrahydropyrimidine; Formate	484.3622		***
FA	2-[2-(5-Bromo-2-methoxybenzylsulfanyl)-5-fluoro-phenyl]-1,4,5,6-tetrahydropyrimidine	409.3222		***
FB	2-[2-(5-Bromo-2-methoxybenzylsulfanyl)-3-fluoro-phenyl]-1,4,5,6-tetrahydropyrimidine	409.3222		***
FC	2-[2-(4,4'-Dimethoxybiphenyl-3-ylmethylsulfanyl)phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	499.4717		**
FD	2-[2-(9H-Fluoren-9-ylsulfanyl)phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	437.4033		**
FE	2-[2-(3'-Chloro-4'-fluoro-4-methoxybiphenyl-3-ylmethylsulfanyl)phenyl]-1,4,5,6-tetrahydropyrimidine; Formate	486.9987		**
FF	2-[2-(1-Naphthalen-1-ylethylsulfanyl)phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	382.9562		***
FG	2-[2-(4-Methoxybiphenyl-3-ylmethylsulfanyl)phenyl]-1,4,5,6-tetrahydropyrimidine; Formate	434.5634		***
FH	2-[2-(5-Bromo-2-methoxybenzylsulfanyl)-5-fluoro-phenyl]-4,5-dihydro-1H-imidazole; Formate	441.3253		***
FI	2-(2-Benzhydrylsulfenyl-phenyl)-1,4,5,6-tetrahydropyrimidine; Formate	404.5372		***

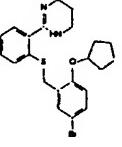
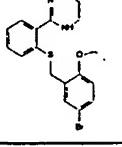
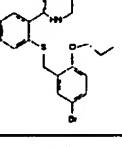
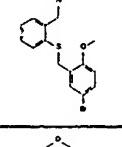
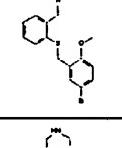
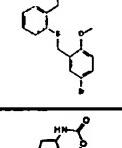
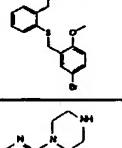
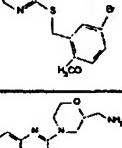
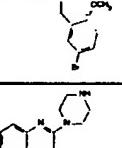
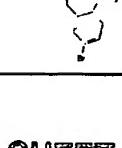
-114-

FJ	2-(3-Amino-propylamino)-6-(5-bromo-2-methoxybenzylsulfanyl)-benzonitrile; Formate	452.3764		*
FK	2-[2-(2-Fluoro-4'-methoxy-[1,1':4',1"]terphenyl-3'-ytmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; formate	528.6517		**
FL	2-[2-(2-Methoxy-5-phenylethynylbenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; Formate	458.5854		**
FM	2-[3-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; Formate	378.4993		*
FN	4-Methoxy-N-(4-methyl-2-(1,4,5,6-tetrahydropyrimidin-2-yl)-phenyl)-benzamide; Formate	369.4248		*
FO	2-(5-Bromo-2-methoxybenzylsulfanyl)-benzamide; formate	397.297		**
FP	4,6-Dimethyl-2-piperazin-1-ylpyrimidine	192.264		*
FQ	8-Isopropyl-3,3-dimethyl-6-piperazin-1-yl-3,4-dihydro-1H-pyranolo[3,4-c]pyridine-5-carbonitrile	314.4308		*
FR	2-Piperazin-1-ylpyrimidine	164.2102		*
FS	1-Pyridin-2-ylpiperazine	163.2224		*

-115-

FT	2-Piperazin-1-yl-4-trifluoromethyl-pyrimidine	232.2085		*
FU	5-Piperazin-1-yl-7-trifluoromethyl-thieno[3,2-b]pyridine-3-carboxylic acid methyl ester	345.3454		*
FV	5-Bromo-2-piperazin-1-yl-pyrimidine	243.1063		*
FW	1-(3-Trifluoromethyl-pyridin-2-yl)-piperazine	231.2207		*
FX	1-(5-Trifluoromethyl-pyridin-2-yl)-piperazine	231.2207		*
FY	Benzyl-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenyl]-amine	265.3581		*
FZ	2-[4-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; Formate	378.4993		**
GA	2-[2-(5-Ethynyl-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; HCl	372.9177		***
GB	2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-1,4,5,6-tetrahydro-pyrimidine; HCl	441.8186		**
GC	2-[2-(5-tert-Butyl-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; HCl	405.0032		*

-116-

GD	2-[2-(5-Bromo-2-cyclopentyloxybenzylsulfanyl)phenyl]-1,4,5,6-tetrahydropyrimidine; Formate	491.4534		***
GE	2-[2-(5-Bromo-2-ethoxybenzylsulfanyl)phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	441.8186		***
GF	2-[2-(5-Bromo-2-propoxybenzylsulfanyl)phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	455.8455		***
GG	[2-(5-Bromo-2-methoxybenzylsulfanyl)benzyl]diethylamine; HCl	430.8357		**
GH	4-[2-(5-Bromo-2-methoxybenzylsulfanyl)benzyl]morpholine; HCl	444.8192		*
GI	1-[2-(5-Bromo-2-methoxybenzylsulfanyl)benzyl]piperazine; Oxalate	497.4145		**
GK	(1-[2-(5-Bromo-2-methoxybenzylsulfanyl)benzyl]pyrrolidin-3-yl)carbamic acid tert-butyl ester	507.4918		*
GL	3-(5-Bromo-2-methoxybenzylsulfanyl)-3,4,5,6-tetrahydro-2H-[1,2]bipyrazinyl	395.3232		*
GM	C-4-[3-(5-Bromo-2-methoxybenzylsulfanyl)-quinoxalin-2-yl]morpholin-2-ylmethylamine; 2HCl	548.3308		**
GN	2-(5-Bromo-2-methoxybenzylsulfanyl)-3-piperazin-1-ylquinoxaline; Formate	491.4131		*

-117-

GO	2-[2-(2-Methoxy-5-methylbenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	362.9226		***
GP	2-[2-(5-Bromo-2-methoxybenzyloxymethyl)phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	425.752		***
GQ	2-[2-(5-(3,3-Dimethyl-but-1-ynyl)-2-methoxybenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	429.0252		*
GR	3-Benzylidene-2-(2-methylaminoethyl)-2,3-dihydroisoindol-1-one	278.3538		*
GS	2-[2-(2-Naphthalen-1-ylethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine	346.4962		*
GU	[2-(5-Bromo-2-methoxybenzylsulfanyl)-benzyl]dimethylamine; HCl	402.7819		**
GV	2-[2-(5-Bromo-2-isopropoxycarbonylbenzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	455.8455		***
GW	2-[2-(2-Ethoxynaphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	412.9824		***
GX	2-[2-(2-Propoxynaphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	427.0093		***
GY	4-Methoxy-3-[2-(1,4,5,6-tetrahydropyrimidin-2-yl)phenylsulfurylmethyl]-benzonitrile; HCl	373.9055		***

-118-

GZ	1-[4-Methoxy-3-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenylsulfanyl]methyl]-phenyl]-ethanone; Formate	400.503		**
HA	(1-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-pyrrolidin-3-yl)-carbamic acid tert-butyl ester	478.6556		*
HB	2-[2-(Naphthalen-1-ylsulfanyl)methyl]-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	368.9293		***
HC	2-(2-Phenethyl-phenyl)-1,4,5,6-tetrahydropyrimidine; Formate	310.4003		*
HD	1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-piperidine; Formate	452.4167		**
HE	(4-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-morpholin-2-ylmethyl)-carbamic acid tert-butyl ester	508.6819		*
HF	C-[4-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-morpholin-2-yl]-methylamine; 2HCl	481.486		**
HG	1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-pyrrolidin-3-ylamine; 2HCl	480.2959		**
HH	2-[2-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-1H-imidazole	316.4265		*
HI	2-[2-(1-Benzyl-1H-imidazol-2-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine	362.4986		*

-119-

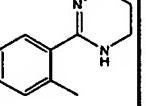
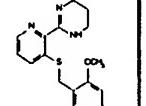
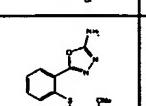
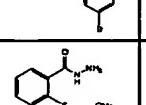
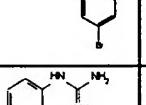
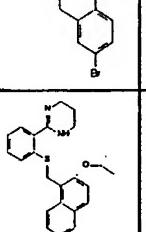
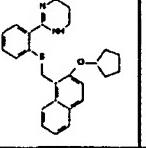
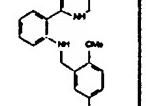
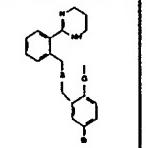
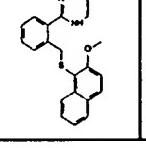
HJ	1-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-pyrazin-2-yl]-pyrrolidin-3-ylamine; 2HCl	468.2446		*
HK	1-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-quinoxalin-2-yl]-pyrrolidin-3-ylamine; 2HCl	518.3045		*
HL	1-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl-benzyl)-pyrrolidin-3-ylamine; HCl	414.9983		**
HM	1-(5-Bromo-2-methoxy-benzyl)-2-phenyl-piperidine	360.2938		*
HN	9-Benzyl-2,3,8,10-tetrahydro-1H-4,9,10a-traza-phenanthrene; Formate	323.3991		*
HO	2-[2-(2-Naphthalen-1-yl-ethoxy-phenyl)-1,4,5,6-tetrahydropyrimidine; Formate	360.4602		***
HP	3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-1,5,6,7,8,8a-hexahydro-imidazo[1,5-a]pyridine; HCl	485.847		***
HQ	3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-5,6,7,7a-tetrahydro-1H-pyrido[1,2-c]imidazole; Formate	481.3901		***
HR	2-{2-(Benzod[b]thiophen-3-ylmethylsulfanyl)-phenyl}-1,4,5,6-tetrahydropyrimidine; HBr	419.4094		***
HS	2-[3-Fluoro-2-(naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; Formate	396.4897		***

-120-

HT	2-(Naphthalen-1-ylmethylsulfanyl)-3-(1,4,5,6-tetrahydropyrimidin-2-yl)-phenylamine; Formate	393.514		**
HU	2-[2-(5-Bromo-2-methoxybenzylsulfanyl)-3-chloro-phenyl]-1,4,5,6-tetrahydropyrimidine	471.8065		***
HV	C-[4-(3-(5-Bromo-2-methoxybenzylsulfanyl)pyrazin-2-yl)-morpholin-2-yl]-methylamine; Formate	471.3795		*
HW	Benzyl-methyl-[2-(1,4,5,6-tetrahydropyrimidin-2-yl)-phenyl]-amine; Formate	325.415		*
HX	2-[2-(2-Methoxyphenylsulfanyl)phenyl]-1,4,5,6-tetrahydropyrimidine, HCl	348.8957		**
HY	1-[2-(5-Bromo-2-methoxybenzylsulfanyl)-phenyl]-5,6-dihydro-4H-pyrimidin-1-yl)-3-methyl-butan-1-one	475.4497		**
HZ	2-[2-(5-Bromo-2-methoxybenzylsulfanyl)-phenyl]-5,6-dihydro-4H-pyrimidine-1-carboxylic acid benzyl	525.4662		**
IA	1-(2-(5-Bromo-2-methoxybenzylsulfanyl)-phenyl)-5,6-dihydro-4H-pyrimidin-1-yl)-2-phenyl-ethanone	509.4668		***
IB	2-[2-(5-Bromo-2-methoxybenzylsulfanyl)-phenyl]-1-methanesulfonyl-1,4,5,6-tetrahydropyrimidine	469.4234		*
IC	2-(5-Bromo-2-methoxybenzylsulfanyl)-phenylamine	324.2413		*

SUBSTITUTE SHEET (RULE 26)

-121-

ID	2-o-Toly-1,4,5,6-tetrahydropyrimidine	174.2456		*
IE	2-[3-(5-Bromo-2-methoxybenzylsulfonyl)-pyridin-2-yl]-1,4,5,6-tetrahydropyrimidine	392.3195		***
IF	5-[2-(5-Bromo-2-methoxybenzylsulfonyl)-phenyl]-[1,3,4]oxadiazol-2-ylamine	392.2762		*
IJ	2-(5-Bromo-2-methoxybenzylsulfonyl)-benzoic acid hydrazide	367.2664		*
IK	N-[2-(5-Bromo-2-methoxybenzylsulfonyl)-phenyl]-guanidine	366.2817		**
IL	2-[2-(2-Isopropoxy-naphthalen-1-methylsulfonyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; Formate	436.5793		**
IM	2-[2-(2-Cyclopentyloxy-naphthalen-1-methylsulfonyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	453.0472		**
IN	(5-Bromo-2-methoxy-phenyl)-[2-(1,4,5,6-tetrahydropyridin-2-yl)-phenyl]-amine	374.2804		**
IO	2-[2-(5-Bromo-2-methoxybenzylsulfonylmethyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; Formate	451.3886		***
IP	2-[2-(2-Methoxy-naphthalen-1-ylsulfonylmethyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	398.9556		***

-122-

IQ	2-[3-(5-Bromo-2-methoxybenzylsulfanyl)pyrazin-2-yl]-1,4,5,6-tetrahydropyrimidine	393.3073		**
IR	2-(3-Chloro-2-(naphthalen-1-ylsulfanyl)methyl)phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	403.374		***
IS	2-[2-(6-Bromo-2-methoxy-naphthalen-1-ylmethylsulfanyl)phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	477.8516		***
IT	9-(5-Bromo-2-methoxy-benzyl)-2,3,9,10-tetrahydro-1H-4,9,10a-triaza-phenanthrene; Formate	432.3214		*
IU	2-[3-Chloro-2-(2-methoxy-naphthalen-1-ylsulfanyl)methyl]phenyl]-1,4,5,6-tetrahydropyrimidine	396.9403		***
IV	2-[2-(2,7-Dimethoxy-naphthalen-1-ylmethylsulfanyl)phenyl]-1,4,5,6-tetrahydropyrimidine; Formate	438.5518		*
IW	2-Piperazin-1-yl-pyridine-3-sulfonic acid ethylamide	270.3557		*
IX	7-Methoxy-3-(4-nitro-phenyl)-2-piperazin-1-yl-quinoline	364.404		*
IY	4-Methyl-2-piperazin-1-yl-quinoline	227.3092		*
IZ	2-[2-(5-Bromo-2-methoxy-phenyl)sulfanyl(methyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	427.7917		***

-123-

JA	2-[2-(5-Bromo-2-methoxy-phenylsulfanylmethyl)-3-chlorophenyl]-1,4,5,6-tetrahydropyrimidine; HCl	462.2365		***
JB	3-(5-Bromo-2-methoxybenzylsulfanyl)-2-(1,4,5,6-tetrahydropyrimidin-2-yl)-quinoline	442.3794		*
JC	2-[1-(2-Naphthalen-1-ylethyl)-1H-pyrol-2-yl]-1,4,5,6-tetrahydropyrimidine	303.407		**
JD	(5-Bromo-2-methoxy-phenyl)-methyl-[2-(1,4,5,6-tetrahydropyrimidin-2-yl)-phenyl]-amine	388.3073		**
JE	[2-(5-Bromo-2-methoxybenzylsulfanyl)-phenyl]-methyl-amine	338.2682		*
JF	2-(5-Bromo-2-methoxybenzylsulfanyl)-benzylamine; HCl	374.7282		**
JK	2-[2-(2-Chlorophenylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	353.3142		**
JL	2-[2-(2-Bromophenylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	397.7655		**
JM	2-(2-o-Tolylsulfanylmethyl-phenyl)-1,4,5,6-tetrahydropyrimidine; HCl	332.8963		**
JN	2-[2-(2,5-Dichlorophenylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	387.7589		***

-124-

JO	2-[3-(3-Chlorobenzylsulfanyl)-5-methyl-isothiazol-4-yl]-1,4,5,6-tetrahydropyrimidine; Formate	383.927		*
JP	N-(4-Methyl-quinazolin-2-yl)-guanidine; HCl	237.691		*
JQ	N-(1-Methyl-benzof)quinazolin-n-3-yl)-guanidine; HCl	287.7509		*
JR	2-[3-(2-Methoxy-naphthalen-1-ylsulfanyl)methyl]-thiophen-2-yl]-1,4,5,6-tetrahydropyrimidine; Formate	414.5537		**
JS	2-[2-(2,5-Dimethoxy-phenylsulfanyl)methyl]-phenyl]-1,4,5,6-tetrahydropyrimidine	342.462		**
JT	2-[2-(4-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	382.9562		***
JU	2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-4,4-dimethyl-4,5-dihydro-1H-imidazole; HCl	459.8091		***
JV	2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-5,5-dimethyl-1,4,5,6-tetrahydropyrimidine; HCl	473.836		***
JW	Methyl-naphthalen-1-yl-[1-(4,5,6-tetrahydropyrimidin-2-yl)-benzyl]-amine; Formate	375.4748		*
JX	Methyl-[2-(1,4,5,6-tetrahydropyrimidin-2-yl)-phenyl]-amine	189.2603		*

-125-

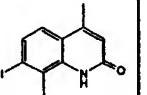
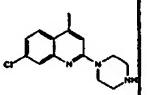
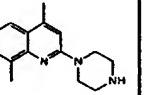
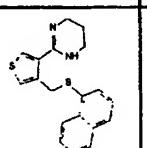
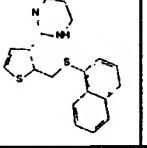
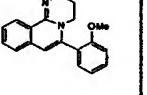
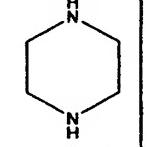
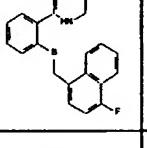
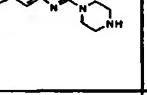
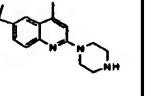
JY	2-(5-Bromo-2-methoxybenzylsulfanyl)-3-(1,4,5,6-tetrahydropyrimidin-2-yl)-quinoxaline	443.3672		*
JZ	2-[3-(Naphthalen-1-ylsulfanyl)methyl]-thiophen-2-yl]-1,4,5,6-tetrahydropyrimidine; Formate	384.5274		***
KA	2-[6-(2-Naphthalen-1-ylethoxy)pyridin-2-yl]-1,4,5,6-tetrahydropyrimidine; Formate	377.4474		*
KB	2-[2-(5-Bromo-2-methoxyphenyl)-ethyl]phenyl]-1,4,5,6-tetrahydropyrimidine	373.2926		***
KC	10-(5-Bromo-2-methoxy-phenyl)-9-methyl-2,3,9,10-tetrahydro-1H,4,9,10a-triaza-phenanthrene; Formate	432.3214		*
KD	2-Morpholin-4-ylmethyl-quinazolin-4-ol	245.2811		*
KE	N,N-Dimethyl-N-(4-phenylquinazolin-2-yl)ethane-1,2-diamine	292.3838		*
KF	4-Phenyl-2-piperazin-1-yl-quinazoline	290.3679		*
KG	2-[3-Chloro-2-(2-naphthalen-1-ylethyl)phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	385.3349		***
KH	2-[2-(5-Bromo-2-methoxyphenyl)-ethyl]-3-fluoro-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	427.7431		***

-126-

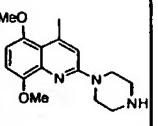
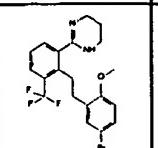
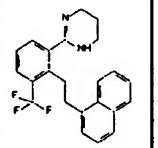
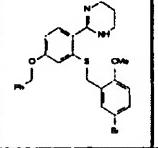
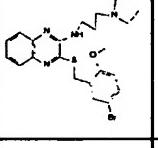
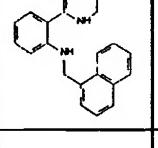
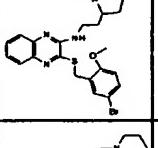
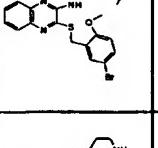
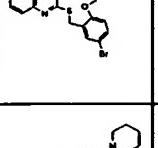
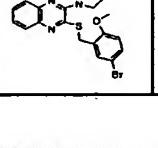
KI	4-(2-Naphthalen-1-yl-ethyl)-6-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-1H-pyridin-2-one; Formate	377.4474		*
KJ	2-[2-(5-Bromo-2-methoxy-phenyl)sulfanyl-methyl]-3-fluoro-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	445.7822		***
KK	2-[2-(Naphthalen-1-ylsulfanyl-methyl)-phenyl]-4,5-dihydro-1H-imidazole; HCl	354.9024		***
KL	2-[3-Fluoro-2-(naphthalen-1-ylsulfanyl-methyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	386.9197		***
KM	2-[3-Bromo-2-(naphthalen-1-ylsulfanyl-methyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	447.8253		***
KN	2-[2-(5-Bromo-2-methoxy-phenyl-ethyl)-3-chloro-phenyl]-1,4,5,6-tetrahydropyrimidine; HCl	444.1974		***
KO	6-Benzylsulfanyl-5-(1,4,5,6-tetrahydropyrimidin-2-yl)-imidazo[2,1-b]thiazole; Formate	374.492		*
KP	2-[3-(5-Bromo-2-methoxy-phenylsulfanyl)-propyl]-1,4,5,6-tetrahydropyrimidine; Formate	389.3177		*
KQ	2-[2-(2-Methoxy-trifluoromethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine	380.4339		***
KR	9-Methyl-10-naphthalen-1-yl-2,3,9,10-tetrahydro-1H-4,9,10a-triaza-phenanthrene; Formate	373.459		*

SUBSTITUTE SHEET (RULE26)

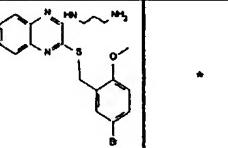
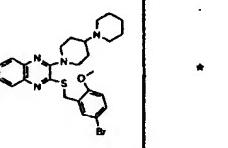
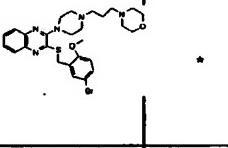
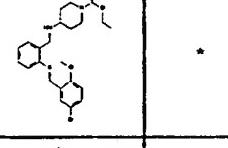
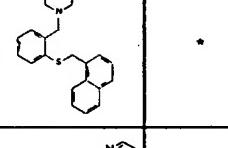
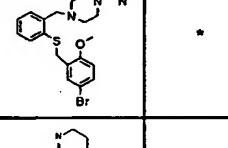
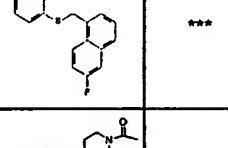
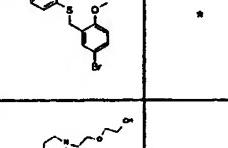
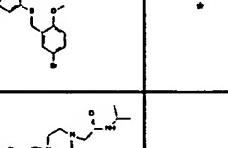
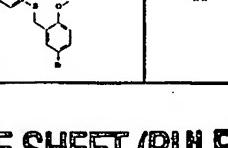
-127-

KS	7-Chloro-4,8-dimethyl-1H-quinolin-2-one	207.6592		*
KT	7-Chloro-4-methyl-2-piperazin-1-yl-quinoline	261.754		*
KU	4,8-Dimethyl-2-piperazin-1-yl-quinoline	241.3361		*
KV	2-[4-(Naphthalen-1-ylsulfanyl)methyl]thiophen-3-yl]-1,4,5,6-tetrahydropyrimidine; HCl	374.9574		**
KW	2-[2-(Naphthalen-1-ylsulfanyl)methyl]thiophen-3-yl]-1,4,5,6-tetrahydropyrimidine; HCl	374.9574		***
KX	6-(2-Methoxyphenyl)-3,4-dihydro-2H-pyrimido[2,1-a]isoquinoline; Formate	336.3948		*
KY	Piperazine	86.1369		*
KZ	2-[2-(4-Fluoronaphthalen-1-ylmethylsulfanyl)phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	431.3717		***
LA	7-Ethyl-4-methyl-2-piperazin-1-yl-quinoline	255.363		*
LB	6-Ethyl-4-methyl-2-piperazin-1-yl-quinoline	255.363		*

-128-

LC	5,8-Dimethoxy-4-methyl-2-piperazin-1-yl-quinoine	287.3618		*
LD	2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-3-trifluoromethyl-phenyl-1,4,5,6-tetrahydro-pyrimidine; Parent	441.2909		***
LE	2-[2-(2-Naphthalen-1-yl-ethyl)-3-trifluoromethyl-phenyl]-1,4,5,6-tetrahydro-pyrimidine; HCl	418.8884		***
LF	2-[4-Benzoyloxy-2-(5-bromo-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; Formate	543.4858		**
LG	[3-(5-Bromo-2-methoxy-benzylsulfanyl)-quinoxalin-2-yl](3-pyrolidin-1-yl-propyl)-amine; formate	533.4937		*
LH	Naphthalen-1-ylmethyl-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenyl]-amine; Formate	361.448		*
LI	[3-(5-Bromo-2-methoxy-benzylsulfanyl)-quinoxalin-2-yl](2-(1-methyl-pyrrolidin-2-yl)-ethyl)-amine; Formate	533.4937		*
LJ	[3-(5-Bromo-2-methoxy-benzylsulfanyl)-quinoxalin-2-yl](3-(2-methyl-piperidin-1-yl)-propyl)-amine; Formate	561.5475		*
LK	[3-(5-Bromo-2-methoxy-benzylsulfanyl)-quinoxalin-2-yl]-piperidin-4-ylmethyl-amine; Formate	519.4669		*
LM	2-[1,4]Bipiperidiny-1'-yl-3-(5-bromo-2-methoxy-benzylsulfanyl)-quinoxaline; Formate	573.5585		*

-129-

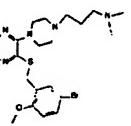
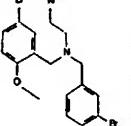
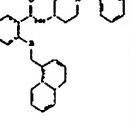
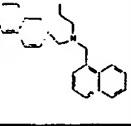
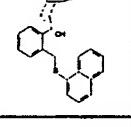
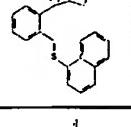
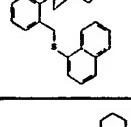
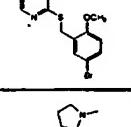
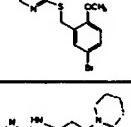
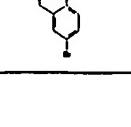
LN	N1-[3-(5-Bromo-2-methoxybenzylsulfanyl)-quinoxalin-2-yl]-propane-1,3-diamine; 2HCl	506.2935		*
LO	2-[1,4"]Bipiperidinyl-1'-y]-3-(5-bromo-2-methoxybenzylsulfanyl)-quinoxaline; Formate	581.5377		*
LP	2-(5-Bromo-2-methoxybenzylsulfanyl)-3-[4-(3-morpholin-4-yl-propyl)-piperazin-1-yl]-quinoxaline; Formate	618.5995		*
LQ	4-[2-(5-Bromo-2-methoxybenzylsulfanyl)-benzylamino]-piperidine-1-carboxylic acid ethyl ester; Formate	539.4949		*
LR	1-[2-(Naphthalen-1-ylmethylsulfanyl)-benzyl]-piperidine	347.5242		*
LS	2-[4-[2-(5-Bromo-2-methoxybenzylsulfanyl)-benzyl]-piperazin-1-yl]-pyrimidino; Formate	531.4779		*
LT	2-[2-(8-Fluoronaphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine; HBr	431.3717		***
LU	1-[4-[2-(5-Bromo-2-methoxybenzylsulfanyl)-benzyl]-piperazin-1-yl]-ethanone; Formate	495.4418		*
LV	2-[2-(4-[2-(5-Bromo-2-methoxybenzylsulfanyl)-benzyl]-piperazin-1-yl)-ethoxy]-ethanol; Formate	541.5108		*
LW	2-[4-[2-(5-Bromo-2-methoxybenzylsulfanyl)-benzyl]-piperazin-1-yl]-N-isopropylacetamide; Formate	552.5371		**

SUBSTITUTE SHEET (RULE26)

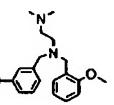
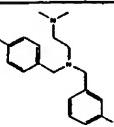
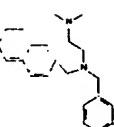
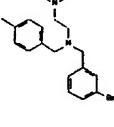
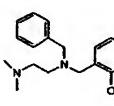
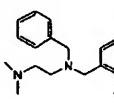
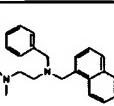
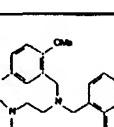
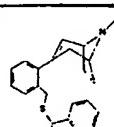
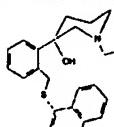
-130-

LX	(1-[2-(5-Bromo-2-methoxybenzylsulfanyl)-benzyl]-2-yl)-methanol; Formate	482.443		***
LY	1-[2-(5-Bromo-2-methoxybenzylsulfanyl)-benzyl]-N-(pyrrolomethyl)-pyrimidine; Formate	521.523		*
LZ	1'-[2-(5-Bromo-2-methoxybenzylsulfanyl)-benzyl]-[1,4]bipiperidiny; Formate	535.5499		*
MA	1-[2-(5-Bromo-2-methoxybenzylsulfanyl)-benzyl]-4-cycloheptylpiperazine; Formate	549.5768		*
MB	3-[2-(1,4,5,6-Tetrahydropyrimidin-2-yl)-phenyl]ethyl-1H-indole	349.437		*
MC	N'-(3-(5-Bromo-2-methoxybenzylsulfanyl)-quinoxalin-2-yl)-N,N-diethyl-ethane-1,2-diamine; Formate	521.4827		*
MD	N-(3-(5-Bromo-2-methoxybenzylsulfanyl)-quinoxalin-2-yl)-N,N-dimethyl-propane-1,3-diamine; Formate	507.4559		*
ME	2-(5-Bromo-2-methoxybenzylsulfanyl)-3-[1,4]diazepan-1-yl-quinoxaline; Formate	505.44		*
MF	N-(4-Bromo-benzyl)-N,N-dimethyl-N-naphthalen-1-ylmethyl-ethane-1,2-diamine	397.358		*
MG	3-(5-Bromo-2-methoxybenzylsulfanyl)-4-(3-morpholin-4-ylpropyl)-3,4,5,6-tetrahydro-2H-[1,2]bipyrazinyl; Formate	568.5396		*

-131-

MH	(3-[3'-(5-Bromo-2-methoxybenzylsulfanyl)-2,3,5,6-tetrahydro[1,2]pyrazinyl-4-yl)-propyl)-dimethyl-amine; Formate	526.5023		*
MI	N-(3-Bromo-benzyl)-N-(5-bromo-2-methoxybenzyl)-N,N-dimethyl-ethane-1,2-diamine	456.2204		*
MJ	N-(1-Benzyl-piperidin-4-yl)-2-(naphthalen-1-ylmethylsulfanyl)-benzamide	466.6471		*
MK	N,N-Dimethyl-N-naphthalen-2-ylmethyl-N-naphthalen-1-ylmethyl-ethane-1,2-diamine	368.5218		*
ML	8-Methyl-3-[2-(naphthalen-1-ylsulfanyl/methyl)-phenyl]-8-azabicyclo[3.2.1]octa-n-3-ol; Formate	435.5915		**
MM	1-Methyl-4-[2-(naphthalen-1-ylsulfanyl/methyl)-phenyl]-piperidin-4-ol; Formate	409.5536		*
MN	3-[2-(Naphthalen-1-ylsulfanyl/methyl)-phenyl]-1-aza-bicyclo[2.2.2]octa-n-3-ol; Formate	421.5646		*
MO	1'-(3-(5-Bromo-2-methoxybenzylsulfanyl)-pyrazin-2-yl)-[1,4]bipiperidinyl	477.4686		*
MP	[3-(5-Bromo-2-methoxybenzylsulfanyl)-pyrazin-2-yl]-2-(1-methyl-pyrroloidin-2-yl-ethyl)-amine	437.4039		*
MQ	[3-(5-Bromo-2-methoxybenzylsulfanyl)-pyrazin-2-yl]-3-(2-methyl-piperidin-1-yl)-propyl-amine	465.4576		*

-132-

MR	N-(3-Chloro-benzyl)-N-(2-methoxy-benzyl)-N,N-dimethyl-ethane-1,2-diamine	332.8731		*
MS	N-(3-Bromo-benzyl)-N,N-dimethyl-N-(4-methyl-benzyl)-ethane-1,2-diamine	381.7429		*
MT	N-(3-Bromo-benzyl)-N,N-dimethyl-N-naphthalen-2-ylmethyl-ethane-1,2-diamine	397.358		*
MU	N-(3-Bromo-benzyl)-N,N-dimethyl-N-(4-methyl-benzyl)-ethane-1,2-diamine	361.325		*
MV	N-Benzyl-N-(2-methoxy-benzyl)-N,N-dimethyl-ethane-1,2-diamine	298.4283		*
MW	N-Benzyl-N-(2-chloro-benzyl)-N,N-dimethyl-ethane-1,2-diamine	302.8468		*
MX	N-Benzyl-N,N-dimethyl-N-naphthalen-1-ylmethyl-ethane-1,2-diamine	318.4619		*
MY	N-(5-Bromo-2-methoxy-benzyl)-N,N-dimethyl-N-naphthalen-1-ylmethyl-ethane-1,2-diamine	427.3843		*
MZ	8-Methyl-3-[2-(naphthalen-1-ylsulfonylmethyl)phenyl]-8-aza-bicyclo[3.2.1]oct-2-ene	371.5462		**
NA	1-Ethyl-3-[2-(naphthalen-1-ylsulfonylmethyl)phenyl]piperidin-3-ol; Formate	423.5805		*

-133-

NB	1-Methyl-4-[2-(naphthalen-1-ylsulfanyl-methyl)-phenyl]-1,2,3,6-tetrahydro-pyridine; Formate	391.5384		**
NC	2-Phenyl-cyclopropanecarboxylic acid (2-dimethylaminoethyl)-naphthalen-1-ylmethyl-amide	372.5102		*
ND	N-Anthracen-9-ylmethyl-N,N-dimethyl-N-naphthalen-1-ylmethyl-ethane-1,2-diamine	418.5817		*
NE	N,N-Dimethyl-N,N'-bis(naphthalen-1-ylmethyl-ethane-1,2-diamine	368.5218		*
NF	N-(2-Methoxy-naphthalen-1-ylmethyl)-N,N-dimethyl-N-naphthalen-1-ylmethyl-ethane-1,2-diamine	398.5481		*
NG	1-[2-(5-Bromo-2-methoxy-benzylsulfonyl)-3-chloro-benzyl]-piperidine	440.8315		*
NH	2-(3-Fluoro-2-(naphthalen-1-yl-ethyl)-phenyl)-1,4,5,6-tetrahydro-pyrimidine; HCl	368.8806		***
NI	3-(3,4-Dichlorophenyl)-1-(2-dimethylaminoethyl)-1-naphthalen-1-ylmethyl-urea	416.3496		*
NJ	3-(3,5-Dichlorophenyl)-1-(2-dimethylaminoethyl)-1-naphthalen-1-ylmethyl-urea	416.3496		*
NK	1-(2-Dimethylaminoethyl)-1-naphthalen-1-ylmethyl-3-(2-trifluoromethyl-phenyl)-urea	415.4584		*

SUBSTITUTE SHEET (RULE 26)

-134-

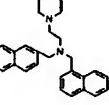
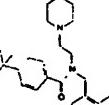
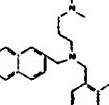
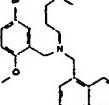
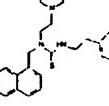
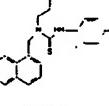
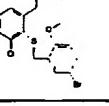
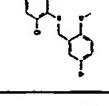
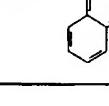
NL	1-(2-Dimethylaminoethyl)-3-(4-methoxy-phenyl)-1-naphthalen-1-ylmethyl-urea	377.4864		*
NM	1-(2-Dimethylaminoethyl)-1-naphthalen-1-ylmethyl-3-phenethyl-urea	375.5139		*
NN	1-(2-Dimethylaminoethyl)-1-naphthalen-1-ylmethyl-3-propyl-urea	313.443		*
NO	1-(2-Dimethylaminoethyl)-3-(4-methoxy-benzyl)-1-naphthalen-1-ylmethyl-urea	391.5133		*
NP	3-(3-Cyano-phenyl)-1-(2-dimethylaminoethyl)-1-naphthalen-1-ylmethyl-urea	372.4699		*
NQ	3-(2,6-Dichloro-pyrido-4-yl)-1-(2-dimethylaminoethyl)-1-naphthalen-1-ylmethyl-urea	417.3374		*
NR	[2-(Naphthalen-2-ylmethysulfanyl)-phenyl]-carbamic acid 2-piperidin-1-yl-ethyl ester; formate	466.6056		*
NS	[2-(Naphthalen-2-ylmethysulfanyl)-phenyl]-carbamic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester; formate	464.5897		*
NT	[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-carbamic acid 2-piperidin-1-yl-ethyl ester	525.4681		**
NU	[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-carbamic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester; formate	523.4522		*

SUBSTITUTE SHEET (RULE26)

-135-

NV	[2-(5-Bromo-2-methoxybenzylsulfanyl)-3-chloro-benzyl]-3-(2-methyl-piperidin-1-yl)-propyl-amine; 2HCl	584.8751		***
NW	1-[2-(5-Bromo-2-methoxybenzylsulfanyl)-3-chloro-benzyl]-piperazine; 2HCl	514.7407		***
NX	1-[2-(5-Bromo-2-methoxybenzylsulfanyl)-3-chloro-benzyl]-pyrrolidin-3-ol; Formate	488.834		*
NY	{1-[2-(5-Bromo-2-methoxybenzylsulfanyl)-3-chloro-benzyl]-pyrrolidin-2-yl}-methanol; Formate	502.8609		*
NZ	1-[2-(5-Bromo-2-methoxybenzylsulfanyl)-3-chloro-benzyl]-azetidine; Formate	458.8077		*
OA	1-[2-(5-Bromo-2-methoxybenzylsulfanyl)-3-chloro-benzyl]-pyrrolidin-3-ol; Formate	488.834		*
OB	[2-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester; Formate	464.5897		*
OC	[2-(2-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester; Formate	478.6166		**
OD	[2-(2-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 2-piperidin-1-yl-ethyl ester; Formate	480.6325		*
OE	{1-[2-(5-Bromo-2-methoxybenzylsulfanyl)-3-chloro-benzyl]-pyrrolidin-2-yl}-methanol; Formate	502.8609		*

-136-

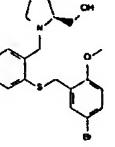
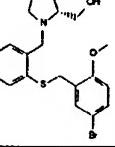
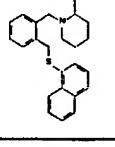
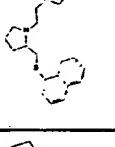
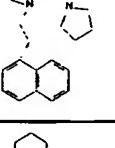
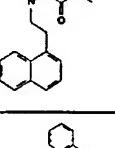
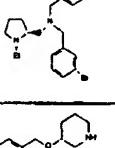
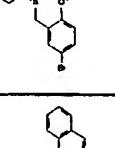
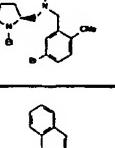
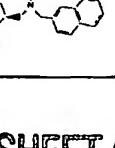
OF	Naphthalen-2-ylmethylnaphthalen-1-ylmethyl-(2-piperidin-1-yl-ethyl)-amine	408.5866		*
OG	4-tert-Butyl-N-naphthalen-1-ylmethyln-(2-piperidin-1-yl-ethyl)-benzamide	428.6177		*
OH	N,N-Dimethyl-N-naphthalen-2-ylmethylnaphthalen-1-ylmethyl-propane-1,3-diamine	382.5487		*
OI	N-(5-Bromo-2-methoxy-benzyl)-N,N-dimethyl-N-naphthalen-1-ylmethyl-propane-1,3-diamine	441.4111		*
OJ	1-Naphthalen-1-ylmethyl-3-phenethyl-1-(2-piperidin-1-yl-ethyl)-thiourea; HCl	468.1052		*
OK	3-[4-Dimethylamino-phenyl]-1-(3-dimethylamino-propyl)-1-naphthalen-1-ylmethyl-thiourea; HCl	457.082		***
OL	4-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chlorobenzylamino]-piperidine-1-carboxylic acid ethyl ester; Formate	573.9397		**
OM	1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chlorobenzyl]-pyrrolidin-3-ylamine; 2HCl	514.7407		***
ON	2-[2-(2-Naphthalen-1-yl-ethyl)-phenyl]-ethylamine; HCl	311.8535		**
OO	Naphthalene-2-sulfonic acid (2-dimethylaminoethyl)-naphthalen-1-ylmethyl-amide	418.5597		*

SUBSTITUTE SHEET (RULE 26)

-137-

OP	1-[2-(5-Bromo-2-methoxybenzylsulfonyl)-3-chloro-benzyl]-2-methoxymethyl-pyrrolidine; Formate	516.8877		*
OQ	(2-Hexyloxy-phenyl)-carbamic acid 2-piperidin-1-yl-1-piperidin-1-ylmethyl-ethyl ester; Formate	491.6758		**
OR	3-[2-(5-Bromo-2-methoxybenzylsulfonyl)-benzyloxy]-pyrrolidine; HCl	444.8192		**
OS	3-[2-(5-Bromo-2-methoxybenzylsulfonyl)-benzyloxy]-pyrrolidine; HCl	444.8192		**
OT	2-[2-(5-Bromo-2-methoxybenzylsulfonyl)-benzyloxymethyl]-pyrrolidine; HCl	458.8461		**
OU	2-[2-(Naphthalen-1-ylsulfonylmethyl)-phenyl]-piperidine; HCl	369.9574		*
OV	3-[2-(5-Bromo-2-methoxybenzylsulfonyl)-benzylamino]-propan-1-ol	396.3482		*
OW	3-[2-(5-Bromo-2-methoxybenzylsulfonyl)-benzylamino]-3-methyl-butan-1-ol	424.402		**
OX	1-[2-(5-Bromo-2-methoxybenzylsulfonyl)-benzyl]-pyrrolidin-3-ol	408.3592		*
OY	1-[2-(5-Bromo-2-methoxybenzylsulfonyl)-benzyl]-pyrrolidin-3-ol	408.3592		*

-138-

OZ	(1-[2-(5-Bromo-2-methoxybenzylsulfanyl)-benzyl]pyrrolidin-2-yl)-methanol	422.3861		*
PA	{1-[2-(5-Bromo-2-methoxybenzylsulfanyl)-benzyl]pyrrolidin-2-yl}-methanol	422.3861		*
PB	{1-[2-(Naphthalen-1-ylsulfanylmethyl)-benzyl]piperidin-2-yl}-methanol; Formate	423.5805		*
PC	2-[2-(Naphthalen-1-ylsulfanylmethyl)pyrrolidin-1-yl]-ethyl-N-pyrrolidine; Formate	386.5628		*
PD	N-pyrrolyl[1-(2-naphthalen-1-yl-ethyl)-pyrrolidin-2-ylmethyl]-amine	308.4668		*
PE	1-(2-Naphthalen-1-yl-ethyl)-piperidine-2-carboxylic acid methyl ester	297.3972		*
PF	(3-Bromo-benzyl)(1-ethyl-pyrrolidin-2-ylmethyl)-naphthalen-1-ylmethylaniline	437.4227		*
PG	3-[2-(5-Bromo-2-methoxybenzylsulfanyl)-benzyloxy]-piperidine; HCl	458.8461		**
PH	(5-Bromo-2-methoxy-benzyl)-(1-ethyl-pyrrolidin-2-ylmethyl)-naphthalen-1-ylmethylaniline	467.449		*
PI	(1-Ethyl-pyrrolidin-2-ylmethyl)-naphthalen-2-ylmethylnaphthalen-1-ylmethylaniline	408.5866		*

-139-

PJ	2-[2-(5-Bromo-2-methoxybenzylsulfanyl)-benzyl]methanol; HCl	458.8461		**
PK	(3-Bromo-benzyl)-(3-imidazol-1-yl-propyl)-naphthalen-1-ylmethyl-amine	434.3788		*
PL	(3-Imidazol-1-yl-propyl)-naphthalen-2-ylmethyl-naphthalen-1-ylmethyl-amine	405.5426		*
PM	[2-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 2-piperidin-1-yl-1-piperidin-1-ylmethyl-ethyl ester; Formate	563.7657		*
PN	[2-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 2-dimethylaminoethyl ester; Formate	426.5408		*
PO	1-[2-(Naphthalen-1-ylsulfanylmethyl)-benzyl]-piperazine; Formate	394.542		**
PP	[3-(2-Methyl-piperidin-1-yl-propyl)-[2-(naphthalen-1-ylsulfanylmethyl)-benzyl]-amine; Formate	464.6764		**
PQ	1-[3-Chloro-2-(naphthalen-1-ylsulfanylmethyl)-benzyl]-piperazine; HCl	419.4168		**
PR	1-[3-Fluoro-2-(2-naphthalen-1-yl-ethyl)-benzyl]-piperazine; HCl	384.9234		***
PS	(1-[3-Chloro-2-(naphthalen-1-ylsulfanylmethyl)-benzyl]-piperidin-2-yl)-methanol; Formate	458.0253		*

SUBSTITUTE SHEET (RULE26)

-140-

PT	N,N-Dimethyl-N-(2-naphthalen-1-yl-ethyl)-N'-naphthalen-1-ylmethyl-ethane-1,2-diamine; Formate	428.5787		*
PU	(1-[2-(5-Bromo-2-methoxybenzylsulfanyl)-3-chloro-benzyl]-piperidin-2-yl)-methanol	470.8577		*
PV	(1-[2-(2-Naphthalen-1-yl-ethyl)-benzyl]-piperidin-2-yl)-methanol; Formate	405.5414		*
PW	1-[2-(2-Naphthalen-1-yl-ethyl)-benzyl]-piperazine; Formate	376.5029		*
PX	[3-(2-Methyl-piperidin-1-yl)-propyl]-[2-(2-naphthalen-1-yl-ethyl)-benzyl]-amine; Formate	446.6373		*
PY	1-[2-(2-Naphthalen-1-yl-ethyl)-benzyl]-pyrrolidin-3-ylamine; Formate	376.5029		**
PZ	5,5-Dimethyl-2-[2-(2-naphthalen-1-yl-ethyl)-phenyl]-4,5-dihydro-1H-imidazole			***
QA	2-[3-Fluoro-2-(2-naphthalen-1-yl-ethyl)-phenyl]-5,5-dimethyl-4,5-dihydro-1H-imidazole			***
QB	2-[2-(5-Bromo-2-methoxybenzylsulfanyl)-3,5-difluorophenyl]-1,5,6-tetrahydropyrimidine			***
QC	2-[2-(5-Bromo-2-methoxybenzylsulfanyl)-3,5-difluorophenyl]-5,5-dimethyl-4,5-dihydro-1H-imidazole			**

-14-

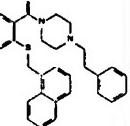
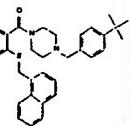
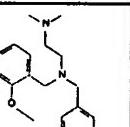
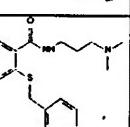
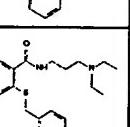
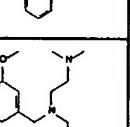
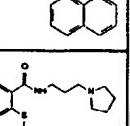
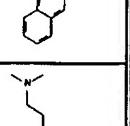
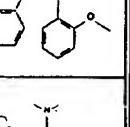
QD	3-(2-Naphthalen-1-yl-ethyl)-2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenylamine		*
QE	Amino-[2-(2-naphthalen-1-yl-ethyl)-phenyl]-acetonitrile		*
QF	1-(2-(2-Naphthalen-1-yl-ethyl)-phenyl)-ethane-1,2-diamine		**
QG	2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-4-methyl-4,5-dihydro-1H-imidazole		**
QH	2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-4-methyl-4,5-dihydro-1H-imidazole		***
QI	2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-phenyl]-4-methyl-4,5-dihydro-1H-imidazole		***
QJ	2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3,4-difluorophenyl]-1,4,5,6-tetrahydropyrimidine		***
QK	2-[3-Fluoro-2-(naphthalen-1-ylsulfanyl)methyl]-phenyl]-5,5-dimethyl-4,5-dihydro-1H-imidazole		**
QL	2-[2-(5-Bromo-2-methoxy-phenyl)-1-methyl-ethyl-phenyl]-1,4,5,6-tetrahydropyrimidine		***
QM	2-(2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-4-trifluoromethyl-phenyl)-4,4-dimethyl-4,5-dihydro-1H-imidazole		*

SUBSTITUTE SHEET (RULE 26)

-142-

QN	2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-4-trifluoromethyl-phenyl]-5,5-dimethyl-1,4,5,6-tetrahydro-pyrimidine			*
QO	2-(3-Methoxy-2-(2-naphthalen-1-ylethyl)-phenyl)-1,4,5,6-tetrahydropyrimidine			***
QP	2-[2-(5-Bromo-2-methoxybenzylsulfanyl)-3-chloro-phenyl]-1,4,5,6-tetrahydropyrimidin-5-ol			***
QQ	2-[2-(5-Bromo-2-methoxy-phenyl-ethyl)-3-methoxy-phenyl]-1,4,5,6-tetrahydropyrimidine			***

TABLE 5

Salt	Molecular Weight	Structure	Salt	Molecular Weight	Structure
Parent	347.5242		Parent	466.6471	
Parent	331.9091		Parent	508.7277	
Parent	333.4453		Parent	377.3244	
Parent	365.4626		Parent	378.5383	
Parent	646.0503		Parent	406.5921	
Formate	513.4192		Parent	348.4882	
Formate	533.4937		Parent	404.5762	
Formate	595.5646		Parent	312.4552	
HCl	525.9799		Parent	348.4882	

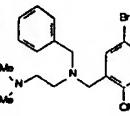
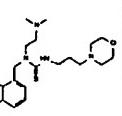
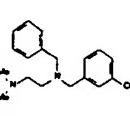
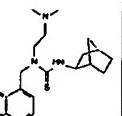
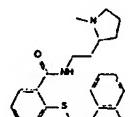
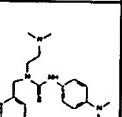
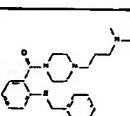
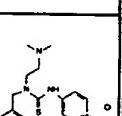
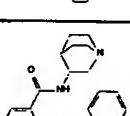
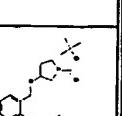
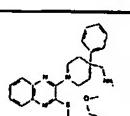
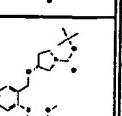
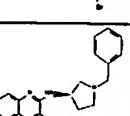
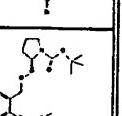
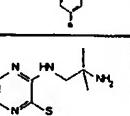
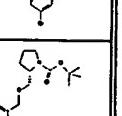
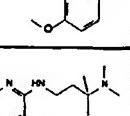
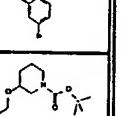
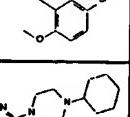
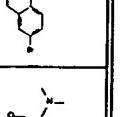
SUBSTITUTE SHEET (RULE 26)

Formate	530.4901		Parent	328.4546	
Formate	599.6367		Parent	372.3079	
Formate	579.5194		Parent	377.3244	
Formate	590.5457		Parent	337.2916	
Formate	568.4987		Parent	458.6678	
Formate	535.5096		Parent	353.5078	
Parent	561.5456		Parent	362.4717	
Formate	559.5316		Formate	468.5781	
Formate	534.4815		Formate	527.4406	
Formate	507.4559		Formate	468.5781	

SUBSTITUTE SHEET (RULE26)

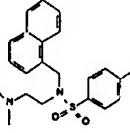
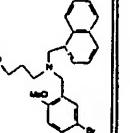
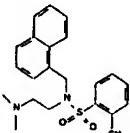
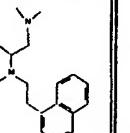
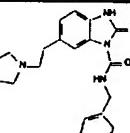
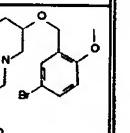
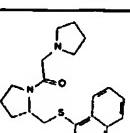
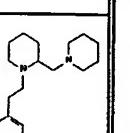
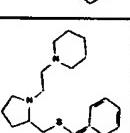
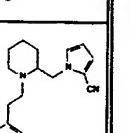
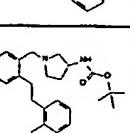
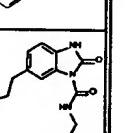
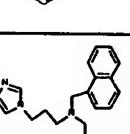
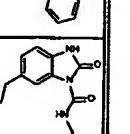
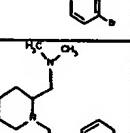
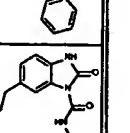
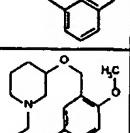
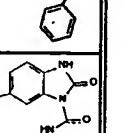
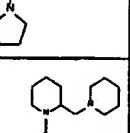
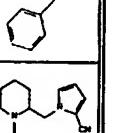
Formate	493.429		Formate	502.8609	
Parent	591.6153		Formate	516.8877	
Parent	527.5285		Formate	482.605	
Formate	483.4339		Parent	321.2376	
Parent	178.2774		Parent	454.6122	
Parent	426.1942		Parent	513.4747	
Parent	392.2957		Parent	432.9709	
Parent	649.6519		Parent	467.449	
Formate	333.2297		Parent	382.5267	
Formate	595.5646		Parent	398.5261	

SUBSTITUTE SHEET (RULE 26)

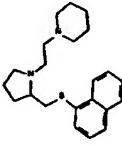
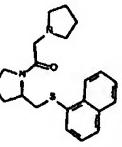
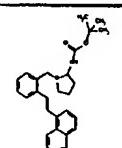
Parent	377.3244		HCl	451.0753	
Parent	298.4283		HCl	418.0454	
Parent	404.5762		HCl	443.0552	
Parent	447.6446		HCl	442.024	
Parent	402.5603		Parent	508.4765	
Parent	549.5346		Parent	508.4765	
Formate	581.5377		Parent	522.5034	
Formate	443.3691		Parent	522.5034	
Formate	485.4497		Parent	522.5034	
Formate	523.4986		Parent	428.5524	

SUBSTITUTE SHEET (RULE 26)

Formate	457.396		Parent	374.528	
Formate	529.4595		Parent	387.5029	
Formate	338.4082		Parent	294.4399	
Formate	340.3808		Parent	353.3024	
Formate	336.3924		HCl	472.873	
Parent	293.4118		Formate	467.388	
Parent	336.4003		Parent	278.3538	
Parent	318.4619		Parent	282.4289	
Parent	454.4283		Parent	378.4742	
Parent	357.4552		Parent	406.528	

Parent	386.4903		Parent	464.4051	
Parent	393.5096		Parent	296.4558	
Parent	364.4473		Formate	443.3855	
Formate	400.5463		Parent	336.5206	
Formate	400.5897		Parent	343.4717	
Parent	430.5902			Not Determined	
	Not Determined			Not Determined	
	Not Determined			Not Determined	
	Not Determined			Not Determined	
	Not Determined			Not Determined	

149

	Not Determined			Not Determined	
	Not Determined				

SUBSTITUTE SHEET (RULE 26)

Example 3: cAMP Assay for MC4-R Antagonist Activity**Method**

MC4 Receptors are expressed in stably transfected K293 cells. The cells
5 are incubated in DMEM base medium (10% FBS, 1X glutamine, and 0.4 mg/ml G418)
at 37°C, in an atmosphere of 6.0% CO₂ and 90% relative humidity. Two days before the
experiment, the cells are trypsinized and 200 µl of the cell suspension (138,000
cells/ml) is deposited into 96-well Costar cell culture plates.

The test compounds are then dissolved in DMSO creating a 30mM stock
10 solution, which is subsequently diluted to 180, 650, 20, 6.6, 2.2 µM in OPTI-MEM
(GIBCO-BRL) media with 50 µM IBMX (isobutylmethylxanthine, Sigma) minutes
before the experiment.

The media is then thoroughly removed from the cell culture plates
through a 12-channel straight manifold. 90 µl of OPTI-MEM media with 50 µM IBMX
15 is added to each well (McHale et al. *FEBS Letters* 345 (1994) 147-150). The plate is
then placed in an incubator set at 37 °C, 6.0% CO₂ and 90% relative humidity. After 15
minutes of incubation, 90 µl of the test compound solutions (or a control solution of
OPTI-MEM and IBMX) are added and the plates are incubated for another 10 minutes.
20 µl of the ligand MSH solution in OPTI-MEM is then added. The cell plates are
20 incubated for an additional hour at 37 °C.

After the incubation, the media mixture is removed by 12-channel
straight manifold. 60 µl of 70% ethanol is added to each well. The plates are then
placed on a shaker for 30 minutes to extract the cAMP. The amount of cAMP is
detected by the cyclic AMP [¹²⁵I] Biotrak SPA screening assay system (Amersham).
25 The system involves adding 50 µl of 1X assay buffer into each well of an OptiPlate-96
(Packard). 50 µl of the tracer solution (cAMP-¹²⁵I) is added into each well. 5 µl of the
cAMP extract is added into the mixture, followed by the addition of cAMP antiserum
and 50 µl of SPA PVT-antibody binding beads. The plates are then covered with
TopSeal-A (Packard) and incubated at room temperature for up to fifteen hours before
30 being analyzed using a TOPCOUNT machine.

Example 4: In Vivo Assay for MC4-R Antagonist Activity

The following *in vivo* assay was used to test the effects of MC4-R antagonists on mice.

Male lean C57BL/6J mice were individually housed in macrolon cages ($22 \pm 5^{\circ}\text{C}$; 12:12 h light/dark cycle with lights off at 6 pm). Tap water and mouse chow diet were given *ad libitum*. Mice were stereotactically implanted with a chronic guide cannula aimed to the third ventricle (intracerebroventricular) one week prior to testing.

It had been previously determined that food deprived lean mice which had been injected with 0.1 nmol of MT II (a MC4-R agonist) prior to refeeding showed decreased feeding response within 1 hour of injection (Figure 1). In previous experiments using peptidic MC4-R antagonists, it has been shown that the decreased feeding response of MT II treated food-deprived mice can be reversed by the intracerebroventricular injection of MC4-R antagonists.

In this experiment, food deprived lean mice were injected 15 intracerebroventricularly with either Compound N or Compound O, at a dose of 15 nmol prior to injection of MT II at the dose of 0.05 nmol.

The results of the experiment are shown in Figures 2 and 3. Figure 2 shows that administration of 15 nmol of Compound N partially reverses the effect of the administration of the MC4-R agonist, MT II. Figure 3 shows that administration of 20 Compound O did not significantly effect the food intake of mice treated with MT II.

Example 5: cAMP Assay for MC Receptor Agonist Activity (cAMP Assay)

The cAMP assay identifies compounds which have agonist activity against MC receptors. It is used to identify the selectivity of agonist which selectively antagonize receptors of interest. The following method is outlined for MC4-R, but corresponding procedures were used for the other MC receptors, MC1-R, MC3-R, and MC5-R.

Method

MC4 Receptors are expressed in stably transfected HEK293 cells. The cells are 30 incubated in DMEM base medium (10% FBS, 1X glutamine, and 0.4 mg/ml G418) at 37°C, in an atmosphere of 6.0% CO₂ and 90% relative humidity. Two days before the experiment, the cells are trypsinized and 200 µl of the cell suspension (138,000 cells/ml) is deposited into 96-well Costar cell culture plates.

The test compounds are then dissolved in DMSO creating a 30mM stock solution, which is subsequently diluted to 180, 650, 20, 6.6, 2.2 µM in OPTI-MEM (GIBCO-BRL) media with 50 µM IBMX (isobutylmethylxanthine, Sigma) minutes before the experiment.

- 5 The media is then thoroughly removed from the cell culture plates through a 12-channel straight manifold. 90 µl of OPTI-MEM media with 50 µM IBMX is added to each well (McHale et al. *FEBS Letters* 345 (1994) 147-150). The plate is then placed in an incubator set at 37 °C, 6.0% CO₂ and 90% relative humidity. After 15 minutes of incubation, 90 µl of the test compound solutions (or a control solution of OPTI-MEM
10 and IBMX) are added and the plates are incubated for another 10 minutes. 20 µl of the ligand MSH solution in OPTI-MEM is then added. The cell plates are incubated for an additional hour at 37 °C.

- After the incubation, the media mixture is removed by 12-channel straight manifold. 60 µl of 70% ethanol is added to each well. The plates are then placed on a
15 shaker for 30 minutes to extract the cAMP. The amount of cAMP is detected by the cyclic AMP [¹²⁵I] Biotrak SPA screening assay system (Amersham). The system involves adding 50 µl of 1X assay buffer into each well of an OptiPlate-96 (Packard). 50 µl of the tracer solution (cAMP-¹²⁵I) is added into each well. 5 µl of the cAMP extract is added into the mixture, followed by the addition of cAMP antiserum and 50 µl
20 of SPA PVT-antibody binding beads. The plates are then covered with TopSeal-A (Packard) and incubated at room temperature for up to fifteen hours before being analyzed using a TOPCOUNT machine.

Compounds O, N, AG, AL, and AM were found to be at least 100 fold more selective for MC4-R than MC1-R, MC3-R and MC5-R.

25 **INCORPORATION BY REFERENCE**

The entire contents of all references and patents cited herein are hereby incorporated by reference. The entire contents of U.S. Patent 5,908,609 and all its references also expressly incorporated herein.

EQUIVALENTS

- 30 Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments and methods described herein. Such equivalents are intended to be encompassed by the

-153-

scope of the following claims.

CLAIMS

1. A method for treating a MC4-R associated state in a mammal comprising
administering an effective amount of a MC4-R binding compound to a mammal, such
5 that the MC4-R associated state is treated, wherein said compound is of the formula (I):



wherein

B is an anchor moiety;

Z is a central moiety; and

10 E is a MC4-R interacting moiety.

2. A method for treating an MC4-R associated state in a mammal comprising
administering an effective amount of a MC4-R binding compound to a mammal, such
that the MC4-R associated state is treated, wherein said compound is of the formula
15 (III):



wherein:

B is an anchor moiety;

L₁ and L₂ are linking moieties;

20 A is a cyclic moiety; and

E is a MC4-R interacting moiety.

3. A method for treating an MC4-R associated state in a mammal comprising
administering an effective amount of a MC4-R binding compound to said mammal, such
25 that the MC4-R associated state is treated, wherein said compound is an MC4-R
antagonist, and is of the formula (III):



wherein

B is substituted or unsubstituted biaryl, unsubstituted or substituted heterocyclic,
30 or unsubstituted or substituted phenyl, wherein one or more of said substituents are
halogens, alkyl, alkynyl, alkoxy, aryl, amino, cyano, or nitro;

L₁ is a covalent bond, C₁-C₆ branched or unbranched alkyl, wherein one or two
of the carbons are optionally replaced with oxygen, sulfur or nitrogen atoms;

L₂ is a covalent bond, substituted or unsubstituted amino, ether, thioether, or alkyl;

E is substituted or unsubstituted alkyl, amino, amidino, guanidino, heterocyclic, or aryl, wherein said substituents are amino, arylalkyl, aminoalkyl, alkyl, aryl, alkenyl, 5 or alkynyl; and

A is a substituted or unsubstituted phenyl, heteroaryl, cycloalkyl, or biaryl, and pharmaceutically acceptable salts thereof.

4. The method of any one of claims 1-3, wherein said compound binds to the MC4-
10 R with an IC₅₀ of about 5 μM or less.

5. The method of claim 4, wherein said compound binds to the MC4-R with an IC₅₀ of about 1 μM or less.

15 6. The method of claim 5, wherein said compound binds to the MC4-R with an IC₅₀ of about 0.5 μM or less.

7. The method of claim 6, wherein said compound binds to the MC4-R with an IC₅₀ of about 0.1 μM or less.

20 8. The method of claim 7, wherein said compound binds to the MC4-R with an IC₅₀ of about 0.05 μM or less.

9. The method of claim 8, wherein said compound binds to the MC4-R with an IC₅₀
25 of about 0.03 μM or less.

10. The method of any one of claims 1-9, wherein said compound is an antagonist of
the MC4-R.

30 11. The method of any one of claims 1-9, wherein said compound is an agonist of
the MC4-R.

12. The method of any one of claims 1-11, wherein said effective amount is effective to treat a disorder associated with pigmentation or weight loss.
13. The method of claim 12, wherein said effective amount is effective to treat a disorder associated with weight loss.
5
14. The method of claim 13, wherein said weight loss is a result of anorexia nervosa, old age, cancer cachexia, HIV cachexia, or weightlessness.
- 10 15. The method of any one of claims 1-14, wherein said mammal is a human.
16. The method of any one of claims 1-15, wherein B is substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, or heterocyclic.
- 15 17. The method of claim 16, wherein B is aryl.
18. The method of claim 17, wherein B is carbocyclic.
19. The method of claim 18, wherein B is phenyl.
20
20. The method of claim 19, wherein B is substituted with at least one substituent, wherein each substituent is independently selected from the group consisting of halogens, alkoxy, hydroxy, alkylcarbonyl, cyano, nitro, thiol, alkyl, alkenyl, alkynyl, aryl, arylalkynyl, or arylalkyl.
25
21. The method of claim 20, wherein B is substituted with at least one halogen.
22. The method of claim 20, wherein B is substituted with at least one alkoxy group.
30
23. The method of claim 20, wherein B is substituted with at least one alkyl group.
24. The method of claim 16, wherein B comprises more than one aromatic ring.

25. The method of claim 24, wherein B is substituted or unsubstituted naphthyl, fluorene, anthracene, or biphenyl.
26. The method of claim 25, wherein B is substituted or unsubstituted naphthyl.
5
27. The method of claim 25, wherein B is substituted with one or more substituents selected from the group consisting of halogens, alkoxy, hydroxy, alkylcarbonyl, cyano, nitro, thiol, alkyl, alkenyl, alkynyl, aryl, arylalkynyl, or arylalkyl.
- 10 28. The method of claim 16, wherein B comprises a heterocycle.
29. The method of claim 27, wherein B is substituted or unsubstituted furanyl, imidazolyl, benzothiophenyl, benzofuranyl, quinolinyl, isoquinolinyl, benzodioxanyl, benzoaxazolyl, benzothiazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, piperidinyl, 15 indolyl, thienyl, pyrimidyl, pyrazinyl, purinyl, or deazapurinyl.
30. The method of any one of claims 2-29, wherein L₁ is a covalent bond or a substituted or unsubstituted chain of one to six atoms.
- 20 31. The method of claim 30, wherein said chain comprises a carbon atom and at least one other atom selected from the group consisting of carbon, sulfur, oxygen, or nitrogen.
32. The method of claim 31, wherein said chain comprises a sulfur atom.
- 25 33. The method of claim 31, wherein said chain comprises an oxygen atom.
34. The method of claim 31, wherein said chain comprises two carbon atoms.
35. The method of any one of claims 2-34, wherein A is substituted or unsubstituted
30 phenyl, heteroaryl, or bicyclic.
36. The method of claim 35, wherein A is unsubstituted phenyl.

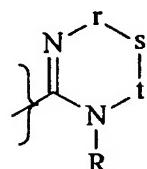
37. The method of claim 36, wherein A is substituted phenyl.
38. The method of claim 37, wherein A is substituted with one or more substituents selected from the group consisting chlorine, fluorine, bromine, iodine, amino, cyano, 5 alkoxy, or alkyl.
39. The method of claim 38, wherein A is substituted with chlorine.
40. The method of claim 38, wherein A is substituted with fluorine.
10
41. The method of claim 38, wherein said alkyl group is methyl or trifluoromethyl.
42. The method of claim 35, wherein A is heteroaryl and selected from the group consisting of pyrimidyl, pyrazinyl, thienyl, pyrrolyl, imidazolyl, or quinoxalinyl.
15
43. The method of any one of claims 2-42, wherein L₂ is selected from the group consisting of a covalent bond, a carbonyl moiety, a thiocarbonyl moiety or C₁-C₆ branched or unbranched alkyl, wherein one, two or three of the carbons are optionally replaced with oxygen, sulfur or nitrogen atoms.
20
44. The method of claim 43, wherein L₂ is a covalent bond.
45. The method of any one of claims 1-42, wherein E is a substituted or unsubstituted amino group, alkyl, cyano, guanidino, amidino, or a heterocyclic moiety.
25
46. The method of claim 45, wherein E is dialkylamino.
47. The method of claim 45, wherein E is heterocyclic.
- 30 48. The method of claim 47, wherein E contains a nitrogen atom.

49. The method of claim 48, wherein E is substituted or unsubstituted piprazinyl, imidoazopyridinyl, pyrroloimidazolyl, pyrrolyl, azetidinyl, azapanyl, diazapanyl, pyrimidinyl, pyridinyl, morpholinyl, or piperidinyl.

5 50. The method of claim 47, wherein E is multicyclic.

51. The method of claim 50, wherein E is a bridged or fused ring.

52. The method of claim 47, wherein E is of the formula (XIII):



10

(XIII)

wherein

r is a covalent bond, CH, CH₂, CR¹, CR¹R², or H;

t is CH, CH₂, CR³, CR³R⁴, or H;

s is CH, CH₂, alkenyl, CHR⁵, CR⁵R⁶, or absent;

15

R is hydrogen, alkyl, alkenyl, arylalkyl, benzocarbonyl,

arylalkylcarbonyl, alkylcarbonyl, optionally linked to A, B, L₁, L₂, R¹, R², R³, R⁴, R⁵, or R⁶ to form a ring; and

20

R¹, R², R³, R⁴, R⁵, and R⁶ are each halogen, thiol, alkoxy, alkyl, alkenyl, alkynyl, heterocyclic, aryl, hydroxyl, nitro, amino, cyano, optionally linked to form a ring with R, R¹, R², R³, R⁴, R⁵, or R⁶.

53. The method of claim 52, wherein each of r, s and t are CH₂.

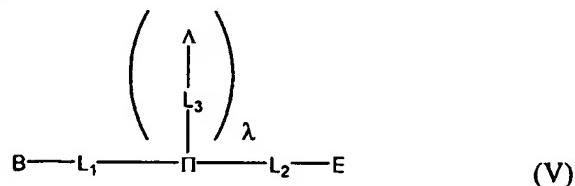
25

54. The method of claim 52, wherein R is H, alkyl, benzocarboxy, alkylcarboxy, or arylalkylcarboxy.

55. The method of claim 52, wherein r is a covalent bond.

56. A method for treating an MC4-R associated state in a mammal comprising administering an effective amount of a MC4-R binding compound to said mammal, such that the MC4-R associated state is treated, wherein said compound is an MC4-R antagonist, and is of the formula (V):

5



B is substituted or unsubstituted biaryl, unsubstituted or substituted heterocyclic, or unsubstituted or substituted phenyl, wherein one or more of said substituents are halogens, alkyl, alkynyl, alkoxy, aryl, amino, cyano, or nitro;

10 L₁ is a covalent bond, C₁-C₆ branched or unbranched alkyl, wherein one or two of the carbons are optionally replaced with oxygen, sulfur or nitrogen atoms;

L₂ is a covalent bond, substituted or unsubstituted amino, ether, thioether, or alkyl;

15 E is substituted or unsubstituted alkyl, amino, amidino, guanidino, heterocyclic, or aryl, wherein said substituents are amino, arylalkyl, aminoalkyl, alkyl, aryl, alkenyl, or alkynyl;

Pi is a covalent bond, a carbon atom, a nitrogen atom, heterocyclic, alkyl, cycloalkyl, or aryl;

20 L₃ is a covalent bond, C₁-C₆ branched, unbranched or cyclic alkyl, wherein one, two or three of the carbons are optionally replaced with oxygen, sulfur or nitrogen atoms, carbonyl, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, or aminothiocarbonyl; and

Pi is heterocyclic, aryl, alkoxy, amino, alkyl, alkenyl, alkynyl, or hydrogen; and λ is 0, 1 or 2, and pharmaceutically acceptable salts thereof.

25

57. The method of claim 56, wherein Pi is a carbon or nitrogen atom.

58. The method of any one of claims 56-57, wherein L₃ is aminocarbonyloxy.

59. The method of any one of claims 56-58, wherein Λ is substituted or unsubstituted aryl.

60. The method of claim 59, wherein Λ is substituted with alkoxy, cyano, halogens ,
5 alkyl, aryl, alkenyl, alkynyl, nitro, or an amino group.

61. The method of any one of claims 56-60, wherein λ is one.

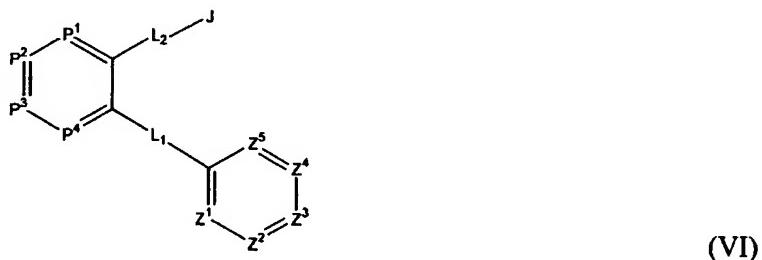
62. The method of any one of claims 56-61, wherein L_1 and L_2 are each CH_2 .
10

63. The method of any one of claim 56-61, wherein B is heterocyclic.

64. The method of any one of claim 56-63, wherein E is heterocyclic or substituted
amino.

15 65. The method of claim 56, wherein Π , L_2 and L_3 together are a single covalent bond.

66. A method for treating an MC4-R associated state in a mammal comprising
20 administering an effective amount of a MC4-R binding compound to a mammal, such that the MC4-R associated state is treated, wherein said compound is an MC4-R antagonist, and is of the formula (VI):



wherein

25 P^1, P^2, P^3, P^4 , and P^5 are optionally substituted carbon, sulfur, or nitrogen, and wherein one of P^1, P^2, P^3, P^4 and P^5 may represent a covalent bond;
 Z^1, Z^2, Z^3, Z^4 , and Z^5 are optionally substituted carbon or nitrogen;

L¹ is a covalent bond, C₁-C₆ branched or unbranched alkyl, wherein one or two of the carbons are optionally replaced with oxygen, sulfur or nitrogen atoms;

L₂ is a covalent bond, substituted or unsubstituted amino, ether, thioether, or alkyl;

5 L₂ is a covalent bond, substituted or unsubstituted amino, ether, thioether, or alkyl; and

J is an unsubstituted or substituted nitrogen containing heterocycle or a substituted or unsubstituted amino group, and pharmaceutically acceptable salts thereof.

10 67. The method of claim 66, wherein P¹, P², P³, P⁴, and P⁵ are each substituted or unsubstituted carbon.

68. The method of claim 67, wherein P¹ and P³ are CH.

15 69. The method of any one of claims 66, 67, or 68 wherein P² and P⁴ are each CH, CF, CCl, CBr, or Cl.

70. The method of any one of claims 66-69, wherein Z³ and Z⁴ are each CH.

20 71. The method of any one claims 66-70, wherein Z¹ is CH, or covalently linked to Z² to form a naphthyl ring;

72. The method of any one of claims 66-70, wherein Z² is CH, C-(C≡CH), CCl, CBr, Cl, CF, or covalently linked to Z¹ to form a naphthyl ring;

25

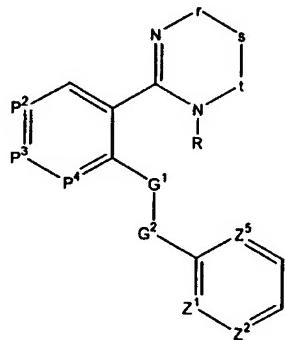
73. The method of any one of claims 66-72, wherein Z⁵ is CH or C-alkoxy.

74. The method of any one of claims 66-73, wherein L² is a covalent bond.

30 75. The method of any one of claims 66-74, wherein J is substituted or unsubstituted piprazinyl, imidoazopyridinyl, pyrroloimidazolyl, pyrrolyl, azetidinyl, azapanyl, diazapanyl, pyrimidinyl, pyridinyl, morpholinyl, or piperidinyl.

76. The method of claim 66, wherein J is a substituted or unsubstituted fused ring or bridged heterocycle.

77. The method of claim 66, wherein said MC4-R binding compound is of the
5 formula (IX):



(IX)

wherein:

P² is CH, CF, CCl, CBr, C-alkyl, C-alkoxy, C-CN, C-OH, or Cl;

P³ is CH, CF, CCl, CBr, C-alkyl, C-alkoxy, C-CN, C-OH, or Cl;

10 P⁴ is CH, CCl, CBr, CF, C-alkyl, C-alkoxy, C-CN, C-OH, or Cl;

G¹ and G² are each independently CH₂, S, or O;

r is a covalent bond or CH₂;

t is CH₂, CR³, or CR³R⁴;

s is CH₂, CHR⁵ or CR⁵R⁶;

15 R is hydrogen or alkyl;

Z¹ is CH, or covalently linked to Z² to form a naphthyl ring;

Z² is CH, C-(C≡CH), CCl, CBr, CI, CF, or covalently linked to Z¹ to
form a naphthyl ring;

Z⁵ is CH, or C-OMe;

20 R³, R⁴, R⁵, and R⁶ are methyl or ethyl, or pharmaceutically acceptable
salts thereof.

78. The method of claim 77, wherein Z¹ is CH, Z² is CBr and Z⁵ is C-OMe.

25 79. The method of claim 77 or 78, wherein P² is CH.

80. The method of any one of claims 77-79, wherein P⁴ is CCl or CF.

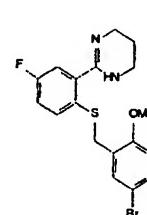
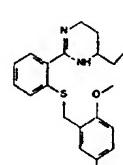
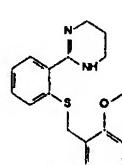
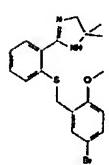
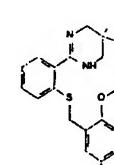
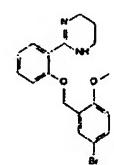
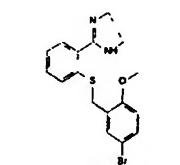
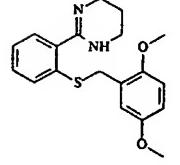
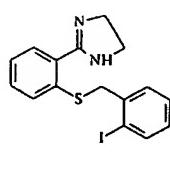
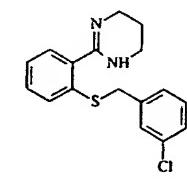
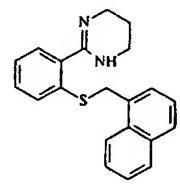
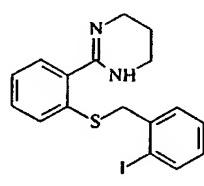
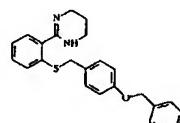
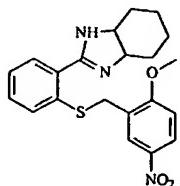
81. The method of any one of claims 77-80, wherein G¹ and G² are each CH₂.

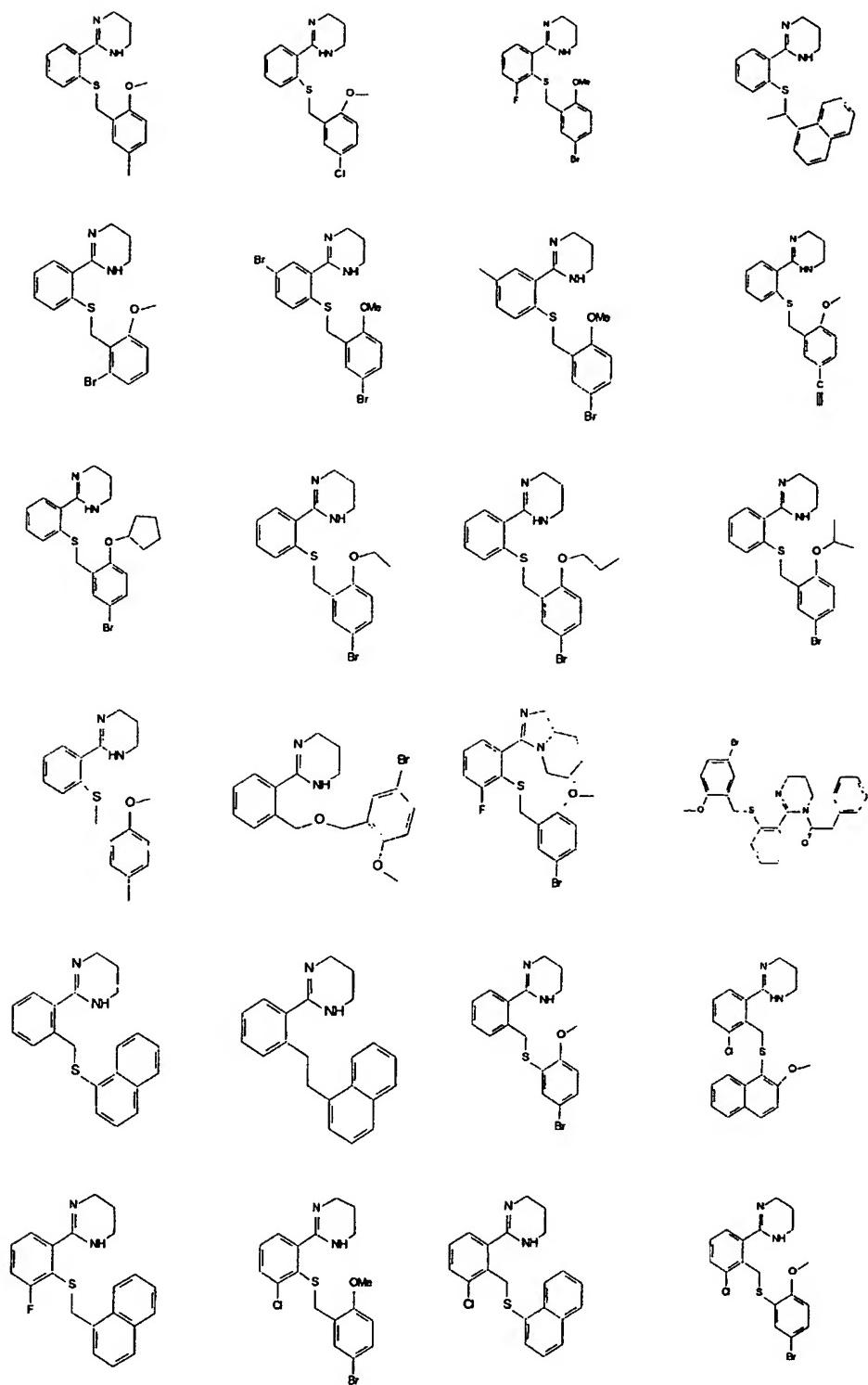
5 82. The method of any one of claims 77-80, wherein G¹ and G² together are -CH₂-S- or -S-CH₂-.

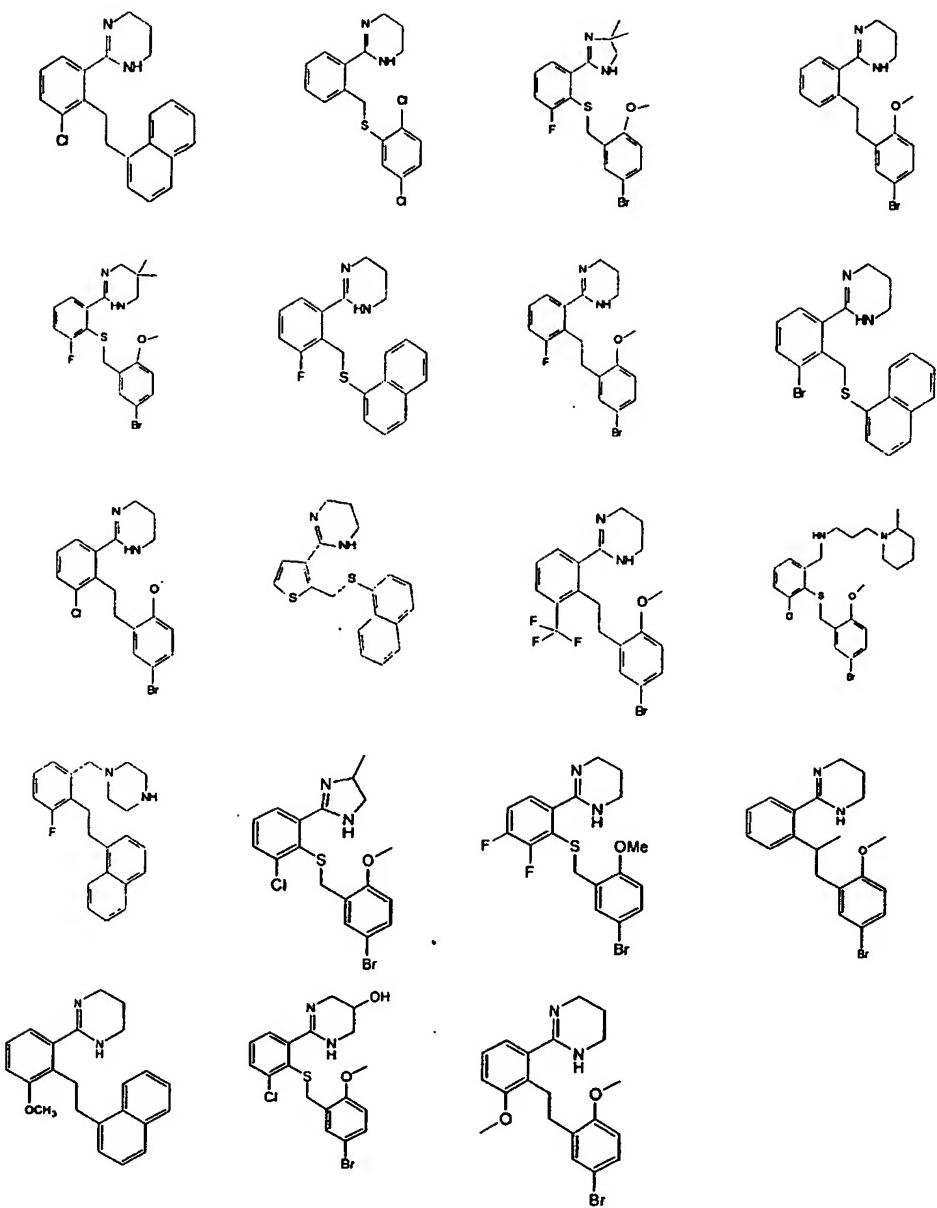
83. The method of any one of claims 73-82, wherein Z¹ and Z² are linked to form a naphthyl ring.

10

84. The method of claim 2, wherein said compound is selected from the group consisting of:







85. The method of claim 2, wherein said compound is selected from the group consisting of: 2-[2-(4-benzyloxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; 2-[2-(2-iodo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 5 2-[2-(2-methoxy-5-nitro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; 2-[2-(naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; 2-[2-(3-chloro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine; 2-[2-(2,5-dimethoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;

- 2-[2-(3-bromo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-iodo-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
2-[2-(2-methoxy-5-nitro-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
2-[2-(2-methoxy-5-nitro-benzyloxy)-phenyl]-1,4,5,6-tetrahydropyrimidine;
- 5 2-[2-(2-bromo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(3-iodo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-methoxy-5-nitro-benzylsulfanyl)-phenyl]-3a,4,5,6,7,7a-hexahydro-1H-
benzoimidazole;
- 10 2-{2-[2-(2-methoxy-naphthalen-1-yl)-ethyl]-phenyl}-1,4,5,6-tetrahydropyrimidine;
- 10 2-[2-(5-bromo-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6,-tetrahydropyrimidine;
2-{2-[2-(2-methyl-naphthalen-1-yl)-ethyl]-phenyl}-1,4,5,6-tetrahydropyrimidine;
2-{2-[2-(2,3-dihydro-benzo[1,4]dioxin-5-yl) -ethyl]-phenyl}-1,4,5,6-
tetrahydropyrimidine;
- 15 2-[2-(2-methoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine;
- 15 2-(2-Benzylsulfanyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine;
2-(2-Pentadecylsulfanyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine;
2-(2-Cyclohexylmethylsulfanyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Methyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 20 2-[2-(3-Nitro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 20 2-[2-(3,5-Dimethoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(4-Fluoro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Chloro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Fluoro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 25 2-[2-(2,4-Bis-trifluoromethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 25 2-[2-(3-Methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(3,5-Bis-trifluoromethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 25 2-[2-(2-Methoxy-5-nitro-benzyloxy)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
- 30 2-(2-Benzylsulfanyl-phenyl)-4,5-dihydro-1H-imidazole;
- 30 2-[2-(2,6-Difluoro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(Naphthalen-1-ylmethoxy)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 30 2-[2-(2-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;

- 1-[2-[2-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-5,6-dihydro-4H-pyrimidin-1-yl]-ethanone;
- 2-[2-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazole;
- 5 2-[2-(2-Iodo-benzylsulfanyl)-phenyl]-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazole;
- 2-[2-(2,5-Dimethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 4-[2-(1,4,5,6-Tetrahydro-pyrimidin-2-yl)-phenylsulfanylmethyl]-quinoline;
- 2-[2-(2-Methoxy-5-nitro-benzylsulfanyl)-pyridin-3-yl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 10 2-[2-(2-Cyclopentyloxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2,3-Dihydro-benzo[1,4]dioxin-5-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(6-Methoxy-2,3-dihydro-benzo[1,4]dioxin-5-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 15 2-[2-(5-fluoro-2-methoxy-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
- 1-Methyl-2-[2-(naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
- 2-[2-(5-Bromo-2-methoxy-benzyloxy)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(Naphthalen-1-yloxymethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 20 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-5,5-dimethyl-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-5,5-dimethyl-4,5-dihydro-1H-imidazole;
- 2-[2-(2,6-Dimethoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 25 2-[2-(2-Bromo-6-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[5-Bromo-2-(5-bromo-2-methoxy-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
- 2-[5-Bromo-2-(5-bromo-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[4-Bromo-2-(5-bromo-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
- 30 pyrimidine;
- 2-[2-(2-Bromo-5-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-5-methyl-phenyl]-1,4,5,6-tetrahydro-pyrimidine;

- 2-[2-(Biphenyl-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(5-Chloro-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Methoxy-5-thiophen-3-yl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
- 5 2-[2-(Biphenyl-2-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(5-Iodo-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-5-fluoro-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
- 10 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
- 15 2-[2-(4,4'-Dimethoxy-biphenyl-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
2-[2-(9H-Fluoren-9-ylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(3'-Chloro-4'-fluoro-4-methoxy-biphenyl-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-
15 tetrahydro-pyrimidine;
- 20 2-[2-(1-Naphthalen-1-yl-ethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-5-fluoro-phenyl]-4,5-dihydro-1H-imidazole;
2-(2-Benzhydrysulfanyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2'-Fluoro-4"-methoxy-[1,1';4',1"]terphenyl-3"-ylmethylsulfanyl)-phenyl]-1,4,5,6-
20 tetrahydro-pyrimidine;
- 25 2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzamidine;
2-[4-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(5-Ethynyl-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-1,4,5,6-tetrahydro-pyrimidine;
- 25 2-[2-(5-Bromo-2-cyclopentyloxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
- 30 2-[2-(5-Bromo-2-ethoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(5-Bromo-2-propoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-diethyl-amine;
- 30 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-piperazine;
C-{4-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-quinoxalin-2-yl]-morpholin-2-yl}-
methylamine;
- 2-[2-(2-Methoxy-5-methyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;

- 2-[2-(5-Bromo-2-methoxy-benzyloxymethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-dimethyl-amine;
2-[2-(5-Bromo-2-isopropoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Ethoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 5 2-[2-(2-Propoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
4-Methoxy-3-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenylsulfanylmethyl]-
benzonitrile;
1-{4-Methoxy-3-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenylsulfanylmethyl]-phenyl}-
ethanone;
- 10 2-[2-(Naphthalen-1-ylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-piperidine;
C-{4-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-morpholin-2-yl}-
methylamine;
1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-pyrrolidin-3-ylamine;
- 15 1-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-pyrrolidin-3-ylamine;
3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-1,5,6,7,8,8a-hexahydro-
imidazo[1,5-a]pyridine;
3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-5,6,7,7a-tetrahydro-1H-
pyrrolo[1,2-c]imidazole;
- 20 2-[2-(Benzo[b]thiophen-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[3-Fluoro-2-(naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-(Naphthalen-1-ylmethylsulfanyl)-3-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenylamine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
- 25 2-[2-(2-Methoxy-phenylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
1-{2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-5,6-dihydro-4H-pyrimidin-1-yl}-
3-methyl-butan-1-one;
1-{2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-5,6-dihydro-4H-pyrimidin-1-yl}-
2-phenyl-ethanone;
- 30 2-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-pyridin-2-yl]-1,4,5,6-tetrahydro-pyrimidine;
N-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-guanidine;
2-[2-(2-Isopropoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;

- 2-[2-(2-Cyclopentyloxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- (5-Bromo-2-methoxy-benzyl)-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenyl]-amine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)methyl]-phenyl]-1,4,5,6-tetrahydro-
- 5 pyrimidine;
- 2-[2-(2-Methoxy-naphthalen-1-ylsulfanyl)methyl]-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-pyrazin-2-yl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[3-Chloro-2-(naphthalen-1-ylsulfanyl)methyl]-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 10 2-[2-(6-Bromo-2-methoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[3-Chloro-2-(2-methoxy-naphthalen-1-ylsulfanyl)methyl]-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 15 2-[2-(5-Bromo-2-methoxy-phenylsulfanyl)methyl]-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-phenylsulfanyl)methyl]-3-chloro-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[1-(2-Naphthalen-1-yl-ethyl)-1H-pyrrol-2-yl]-1,4,5,6-tetrahydro-pyrimidine;
- (5-Bromo-2-methoxy-benzyl)-methyl-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenyl]-
- 20 amine;
- 2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzylamine;
- 2-[2-(2-Chloro-phenylsulfanyl)methyl]-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Bromo-phenylsulfanyl)methyl]-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-(2-o-Tolylsulfanyl)methyl-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 25 2-[2-(2,5-Dichloro-phenylsulfanyl)methyl]-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-(3-Amino-propylamino)-6-(5-bromo-2-methoxy-benzylsulfanyl)-benzonitrile;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-1,4,5,6-tetrahydro-pyrimidine;
- [2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-diethyl-amine;
- 4-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-morpholine;
- 30 3'-(5-Bromo-2-methoxy-benzylsulfanyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl;
- 2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-piperazin-1-yl-6,7-dihydro-quinoxaline;
- 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-piperidine;

- C-{4-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-morpholin-2-yl}-methylamine;
- 1-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-pyrazin-2-yl]-pyrrolidin-3-ylamine;
- 1-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-quinoxalin-2-yl]-pyrrolidin-3-ylamine;
- 5 1-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-pyrrolidin-3-ylamine;
- C-{4-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-pyrazin-2-yl]-morpholin-3-yl}-methylamine;
- 1-[3-Fluoro-2-(2-naphthalen-1-yl-ethyl)-benzyl]-piperazine;
- 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-azetidine;
- 10 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-pyrrolidin-3-ol;
- [2-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester;
- [2-(2-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester;
- 15 [2-(2-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 2-piperidin-1-yl-ethyl ester;
- {1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-pyrrolidin-2-yl}-methanol;
- 4-tert-Butyl-N-naphthalen-1-ylmethyl-N-(2-piperidin-1-yl-ethyl)-benzamide;
- 20 N,N-Dimethyl-N'-naphthalen-2-ylmethyl-N'-naphthalen-1-ylmethyl-propane-1,3-diamine;
- N-(5-Bromo-2-methoxy-benzyl)-N',N'-dimethyl-N-naphthalen-1-ylmethyl-propane-1,3-diamine;
- 1-Naphthalen-1-ylmethyl-3-phenethyl-1-(2-piperidin-1-yl-ethyl)-thiourea;
- 25 3-(4-Dimethylamino-phenyl)-1-(3-dimethylamino-propyl)-1-naphthalen-1-ylmethyl-thiourea;
- 4-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzylamino]-piperidine-1-carboxylic acid ethyl ester;
- 2-[2-(2-Naphthalen-1-yl-ethyl)-phenyl]-ethylamine;
- 30 Naphthalene-2-sulfonic acid (2-dimethylamino-ethyl)-naphthalen-1-ylmethyl-amide;
- 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-2-methoxymethyl-pyrrolidine;
- (2-Hexyloxy-phenyl)-carbamic acid 2-piperidin-1-yl-1-piperidin-1-ylmethyl-ethyl ester;

- 3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyloxy]-pyrrolidine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyloxymethyl]-pyrrolidine;
2-[2-(Naphthalen-1-ylsulfanylmethyl)-phenyl]-piperidine;
3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzylamino]-propan-1-ol;
- 5 3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzylamino]-3-methyl-butan-1-ol;
1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-pyrrolidin-3-ol;
{1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-pyrrolidin-2-yl}-methanol;
{1-[2-(Naphthalen-1-ylsulfanylmethyl)-benzyl]-piperidin-2-yl}-methanol;
2-[2-(Naphthalen-1-ylsulfanylmethyl)-pyrrolidin-1-yl]-ethyl-N-pyrrolidine;
- 10 N-pyrrolyl-[1-(2-naphthalen-1-yl-ethyl)-pyrrolidin-2-ylmethyl]-amine;
1-(2-Naphthalen-1-yl-ethyl)-piperidine-2-carboxylic acid methyl ester;
(3-Bromo-benzyl)-(1-ethyl-pyrrolidin-2-ylmethyl)-naphthalen-1-ylmethyl-amine;
3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyloxy]-piperidine;
(5-Bromo-2-methoxy-benzyl)-(1-ethyl-pyrrolidin-2-ylmethyl)-naphthalen-1-ylmethyl-
- 15 amine;
(1-Ethyl-pyrrolidin-2-ylmethyl)-naphthalen-2-ylmethyl-naphthalen-1-ylmethyl-amine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyloxymethyl]-pyrrolidine;
(3-Bromo-benzyl)-(3-imidazol-1-yl-propyl)-naphthalen-1-ylmethyl-amine;
(3-Imidazol-1-yl-propyl)-naphthalen-2-ylmethyl-naphthalen-1-ylmethyl-amine;
- 20 [2-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 2-piperidin-1-yl-1-piperidin-1-ylmethyl-ethyl ester;
[2-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 2-dimethylamino-ethyl ester;
1-[2-(Naphthalen-1-ylsulfanylmethyl)-benzyl]-piperazine;
[3-(2-Methyl-piperidin-1-yl)-propyl]-[2-(naphthalen-1-ylsulfanylmethyl)-benzyl]-
- 25 amine;
1-[3-Chloro-2-(naphthalen-1-ylsulfanylmethyl)-benzyl]-piperazine;
N,N-Dimethyl-N'-(2-naphthalen-1-yl-ethyl)-N'-naphthalen-1-ylmethyl-ethane-1,2-diamine;
{1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-piperidin-2-yl}-methanol;
- 30 1-[2-(2-Naphthalen-1-yl-ethyl)-benzyl]-piperazine;
[3-(2-Methyl-piperidin-1-yl)-propyl]-[2-(2-naphthalen-1-yl-ethyl)-benzyl]-amine;
1-[3-Fluoro-2-(2-naphthalen-1-yl-ethyl)-benzyl]-piperazine;
{1-[3-Chloro-2-(naphthalen-1-ylsulfanylmethyl)-benzyl]-piperidin-2-yl}-methanol;

- {1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-piperidin-2-yl}-methanol;
{1-[2-(2-Naphthalen-1-yl-ethyl)-benzyl]-piperidin-2-yl}-methanol;
[3-(2-Methyl-piperidin-1-yl)-propyl]-[2-(2-naphthalen-1-yl-ethyl)-benzyl]-amine;
1-[2-(2-Naphthalen-1-yl-ethyl)-benzyl]-pyrrolidin-3-ylamine;
- 5 1-Phenyl-3-piperazin-1-yl-5,6,7,8-tetrahydro-isoquinoline-4-carbonitrile;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-6-ethyl-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(4-Methoxy-biphenyl-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Methoxy-5-phenylethynyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
10 pyrimidine;
- 2-[2-(2-Naphthalen-1-yl-ethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[3-(2-Methoxy-naphthalen-1-ylsulfanylmethyl)-thiophen-2-yl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2,5-Dimethoxy-phenylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 15 2-[2-(4-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-4,4-dimethyl-4,5-dihydro-
1H-imidazole;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-5,5-dimethyl-1,4,5,6-
tetrahydro-pyrimidine;
- 20 2-[3-(Naphthalen-1-ylsulfanylmethyl)-thiophen-2-yl]-1,4,5,6-tetrahydro-pyrimidine;
2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-phenyl}-1,4,5,6-tetrahydro-pyrimidine;
2-[3-Chloro-2-(2-naphthalen-1-yl-ethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-3-fluoro-phenyl}-1,4,5,6-tetrahydro-
pyrimidine;
- 25 2-[2-(5-Bromo-2-methoxy-phenylsulfanylmethyl)-3-fluoro-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
2-[2-(Naphthalen-1-ylsulfanylmethyl)-phenyl]-4,5-dihydro-1H-imidazole;
2-[3-Fluoro-2-(naphthalen-1-ylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[3-Bromo-2-(naphthalen-1-ylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 30 2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-3-chloro-phenyl}-1,4,5,6-tetrahydro-
pyrimidine;
2-[2-(2-Methoxy-5-trifluoromethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;

- 2-[4-(Naphthalen-1-ylsulfanyl-methyl)-thiophen-3-yl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(Naphthalen-1-ylsulfanyl-methyl)-thiophen-3-yl]-1,4,5,6-tetrahydro-pyrimidine;
2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-3-trifluoromethyl-phenyl}-1,4,5,6-tetrahydro-pyrimidine;
- 5 2-[2-(2-Naphthalen-1-yl-ethyl)-3-trifluoromethyl-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(6-Fluoro-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
{1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-piperidin-2-yl}-methanol;
2-[3-Fluoro-2-(2-naphthalen-1-yl-ethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 10 [2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-[3-(2-methyl-piperidin-1-yl)-propyl]-amine;
- 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-pyrrolidin-3-ylamine;
1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-piperazine;
5,5-Dimethyl-2-[2-(2-naphthalen-1-yl-ethyl)-phenyl]-4,5-dihydro-1H-imidazole;
2-[3-Fluoro-2-(2-naphthalen-1-yl-ethyl)-phenyl]-5,5-dimethyl-4,5-dihydro-1H-
- 15 imidazole;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3,5-difluoro-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3,5-difluoro-phenyl]-5,5-dimethyl-4,5-dihydro-1H-imidazole;
- 20 3-(2-Naphthalen-1-yl-ethyl)-2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenylamine;
Amino-[2-(2-naphthalen-1-yl-ethyl)-phenyl]-acetonitrile;
1-[2-(2-Naphthalen-1-yl-ethyl)-phenyl]-ethane-1,2-diamine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-4-methyl-4,5-dihydro-1H-imidazole;
- 25 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-4-methyl-4,5-dihydro-1H-imidazole;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-phenyl]-4-methyl-4,5-dihydro-1H-imidazole;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3,4-difluoro-phenyl]-1,4,5,6-tetrahydro-
- 30 pyrimidine;
2-[3-Fluoro-2-(naphthalen-1-ylsulfanyl-methyl)-phenyl]-5,5-dimethyl-4,5-dihydro-1H-imidazole;

- 2-{2-[2-(5-Bromo-2-methoxy-phenyl)-1-methyl-ethyl]-phenyl}-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy benzyl sulfanyl)-3-fluoro-4-trifluoromethyl-phenyl]-4,4-dimethyl-4,5-dihydro-1H-imidazole;
- 5 2-[2-(5-Bromo-2-methoxy-benzyl sulfanyl)-3-fluoro-4-trifluoromethyl-phenyl]-5,5-dimethyl-1,4,5,6-tetrahydro-pyrimidine;
- 2-[3-Methoxy-2-(2-naphthalen-1-yl-ethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-phenyl]-1,4,5,6-tetrahydro-pyrimidin-5-ol;
- 10 2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-3-methoxy-phenyl}-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-6-ethyl-1,4,5,6-tetrahydro-pyrimidine, and pharmaceutically acceptable salts thereof.
- 15 86. The method of any one of claims 56-85, wherein said compound binds to the MC4-R with an IC₅₀ of about 5 μM or less.
87. The method of claims 86, wherein said compound binds to the MC4-R with an IC₅₀ of about 1 μM or less.
- 20 88. The method of claim 87, wherein said compound binds to the MC4-R with an IC₅₀ of about 0.5 μM or less.
89. The method of claim 88, wherein said compound binds to the MC4-R with an
- 25 IC₅₀ of about 0.1 μM or less.
90. The method of claim 89, wherein said compound binds to the MC4-R with an IC₅₀ of about 0.05 μM or less.
- 30 91. The method of claim 90, wherein said compound binds to the MC4-R with an IC₅₀ of about 0.03 μM or less.

92. The method of any one of claims 56-85, wherein said compound is an antagonist of the MC4-R.

93. The method of any one of claims 56-85, wherein said compound is an agonist of
5 the MC4-R.

94. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said MC4-R binding compound is not 2-[2-(2,5-dichlorothiophen-3-ylmethylsulfanyl)-phenyl]-1, 4, 5, 6-tetrahydropyrimidine.

10

95. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said MC4-R binding compound is not 2[2-(2-chloro- 6-fluoro-benzylsulfanyl)-phenyl]-1, 4, 5, 6-tetrahydropyrimidine.

15

96. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said MC4-R binding compound is not 1-(6-bromo-2-chloro-quinolin-4-yl)-3-(2-diethylaminoethyl)-urea.

97. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said
20 MC4-R binding compound is not 2-[2-(2,6-difluorobenzylsulfanyl)-phenyl]-1, 4, 5, 6-tetrahydropyrimidine.

98. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said
MC4-R binding compound is not 10-[2-(1-methyl-piperadin-2-yl)-ethyl]-2-
25 methylsulfanyl-10H-phenothiazine.

99. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said MC4-R binding compound is not 1-(4-hydroxy-1, 3, 5-trimethyl-piperadin-4-yl)-ethanone.

30

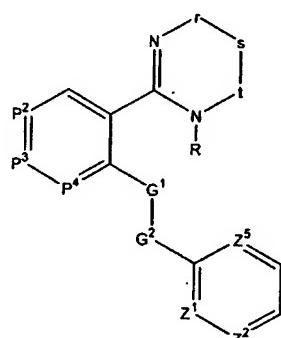
100. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said MC4-R binding compound is not 2-naphthalen-1-ylmethyl-4,5-dihydro-1H-imidazole.

101. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said MC4-R binding compound is not (2,6-dichloro-phenyl)-imidazolidin-2-ylidene-amine.
102. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said
5 MC4-R binding compound is not 2-benzyl-4,5-dihydro-1H-imidazole.
103. The method of any one of claims 1-93 or 138-199 wherein said MC4-R binding compound is not 5-(4-chloro-phenyl)-2,5-dihydro-3H-imidazo[2,1-a]-isoindol-5-ol.
- 10 104. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said MC4-R binding compound is not 4,6-dimethyl-2-piperazin-1-yl-pyrimidine.
- 15 105. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said MC4-R binding compound is not 2-piperazin-1-yl-pyrimidine.
106. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said
MC4-R binding compound is not 1-pyridin-2-yl-piperazine.
107. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said
20 MC4-R binding compound is not 2-piperazin-1-yl-4-trifluoromethyl pyrimidine.
108. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said MC4-R binding compound is not 6-piperazin-1-yl-7-trifluoromethyl-thieno[3,2-b]pyridine-3-carboxylic acid methyl ester.
- 25 109. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said MC4-R binding compound is not 5-bromo-2-piperazin-1-yl)-pyrimidine.
110. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said
30 MC4-R binding compound is not 1-(3-trifluoromethyl-pyridin-2-yl)-piperazine.
111. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said MC4-R binding compound is not 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine.

112. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said MC4-R binding compound is not piperazine.

5 113. The method of any one of claims 1, 2, 3, 56, 66, 77, 138 or 139 wherein said MC4-R binding compound is not (2-Hexyloxy-phenyl)-carbamic acid 2-piperidin-1-yl-1-piperidin-1-ylmethyl-ethyl ester.

114. An MC4-R binding compound of the formula (IX):



(IX)

10

wherein:

P² is CH, CF, CCl, CBr, C-alkyl, C-alkoxy, C-CN, C-OH, or Cl;

P³ is CH, CF, CCl, CBr, C-alkyl, C-alkoxy, C-CN, C-OH, or Cl;

15

P⁴ is CH, CCl, CBr, CF, C-alkyl, C-alkoxy, C-CN, C-OH, or Cl;

G¹ and G² are each independently CH₂, S, or O;

r is a covalent bond or CH₂;

t is CH₂, CR³, or CR³R⁴;

s is CH₂, CHR⁵ or CR⁵R⁶;

20

R is hydrogen or alkyl;

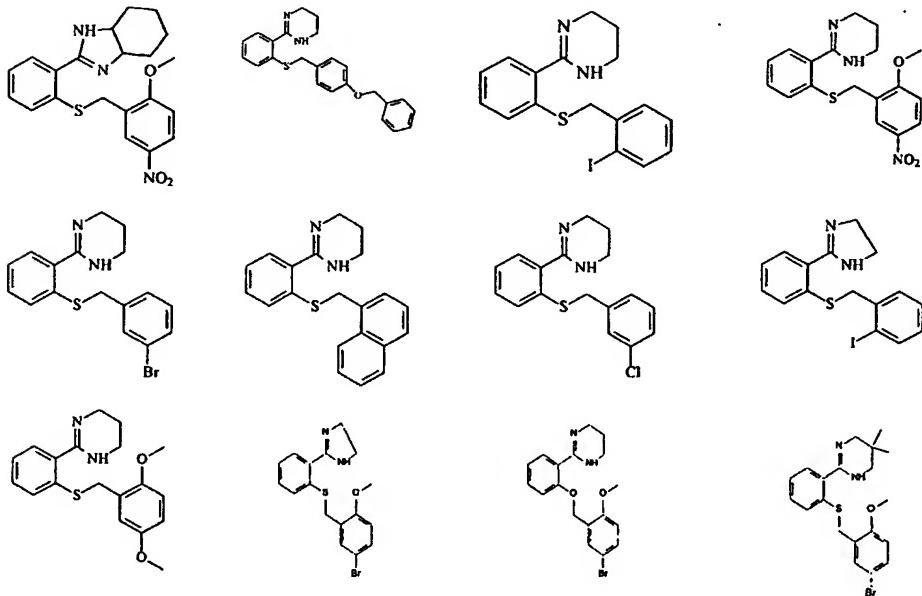
Z¹ is CH, or covalently linked to Z² to form a naphthyl ring;

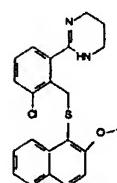
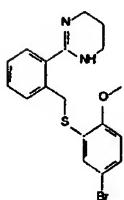
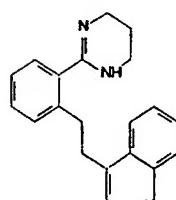
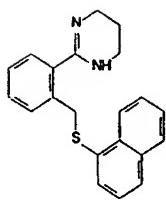
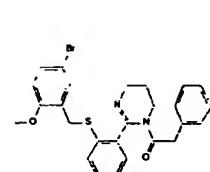
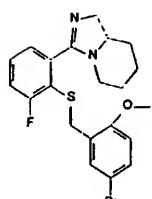
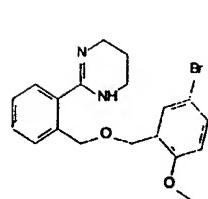
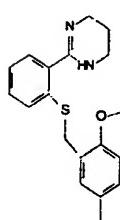
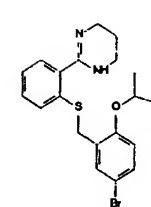
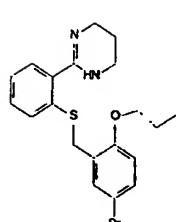
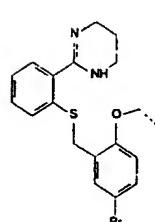
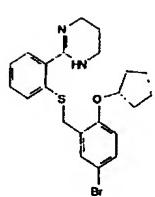
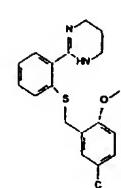
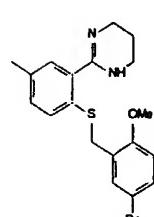
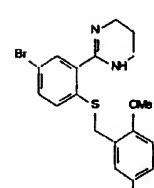
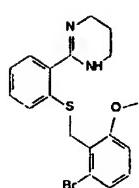
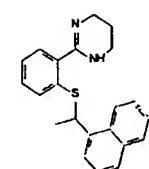
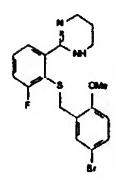
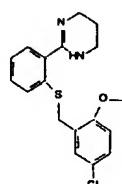
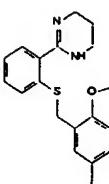
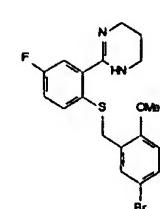
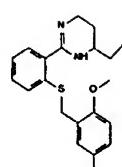
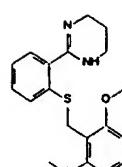
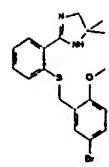
Z² is CH, C-(C≡CH), CCl, CBr, CI, CF, or covalently linked to Z¹ to form a naphthyl ring;

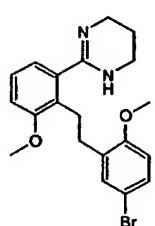
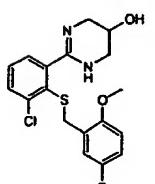
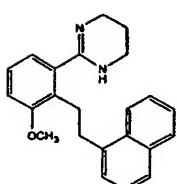
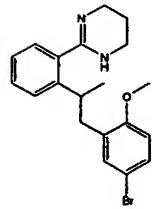
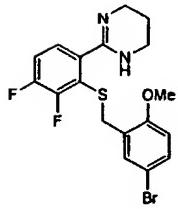
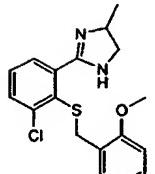
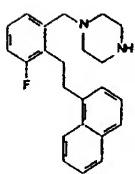
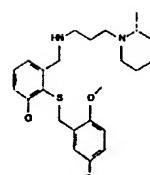
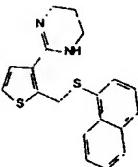
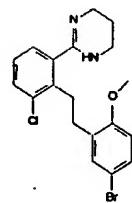
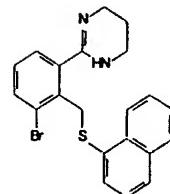
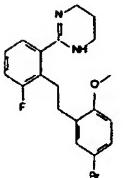
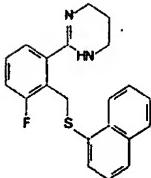
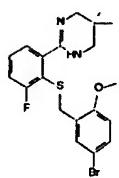
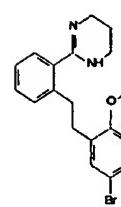
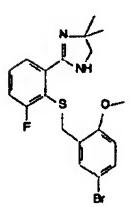
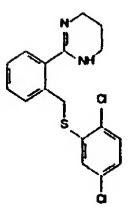
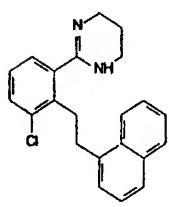
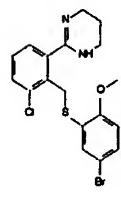
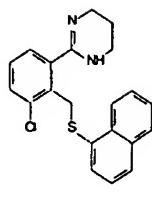
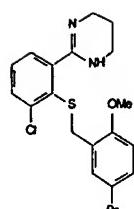
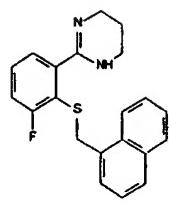
Z⁵ is CH, or C-OMe;

25 R³, R⁴, R⁵, and R⁶ are methyl or ethyl, or pharmaceutically acceptable salts thereof.

115. The compound of claim 94, wherein Z^1 is CH, Z^2 is CBr and Z^5 is C-OMe.
116. The compound of claim 114-115, wherein P^2 is CH.
- 5 117. The compound of claim 114-116, wherein P^4 is CCl or CF.
118. The compound of claim 114-117, wherein G^1 and G^2 are each CH₂.
- 10 119. The compound of claim 114-117, wherein G^1 and G^2 together are -CH₂-S- or -S-CH₂-.
120. The compound of claim 114-119, wherein Z^1 and Z^2 are linked to form a naphthyl ring.
- 15 121. An MC4-R binding compound, wherein said compound is selected from the group consisting of:







122. The MC4-R binding compound of any one of claims 114-121, wherein said compound is not 2-[2-(2,5-dichlorothiophen-3-ylmethylsulfanyl)-phenyl]-1, 4, 5, 6-tetrahydropyrimidine.

5 123. The MC4-R binding compound of any one of claims 114-121, wherein said compound is not 2-[2-(2,6-difluorobenzylsulfanyl)-phenyl]-1, 4, 5, 6-tetrahydropyrimidine.

10 124. A pharmaceutical composition for the treatment of a MC4-R associated state in a mammal comprising a pharmaceutically acceptable carrier and an effective amount of an MC4-R binding compound of the formula (I):



wherein

B is an anchor moiety;

15 Z is a central moiety;

E is a MC4-R interacting moiety; and

pharmaceutically acceptable salts thereof.

20 125. A pharmaceutical composition for the treatment of a MC4-R associated state in a mammal comprising a pharmaceutically acceptable carrier and an effective amount of an MC4-R binding compound of the formula (III):



wherein:

B is an anchor moiety;

25 L₁ and L₂ are linking moieties;

A is a cyclic moiety; and

E is a MC4-R interacting moiety.

30 126. A pharmaceutical composition for the treatment of a MC4-R associated state in a mammal comprising a pharmaceutically acceptable carrier and an effective amount of an MC4-R binding compound of the formula (III):



wherein

B is substituted or unsubstituted biaryl, unsubstituted or substituted heterocyclic, or unsubstituted or substituted phenyl, wherein one or more of said substituents are halogens, alkyl, alkynyl, alkoxy, aryl, amino, cyano, or nitro;

5 L₁ is a covalent bond, C₁-C₆ branched or unbranched alkyl, wherein one or two of the carbons are optionally replaced with oxygen, sulfur or nitrogen atoms;

L₂ is a covalent bond, substituted or unsubstituted amino, ether, thioether, or alkyl;

10 E is substituted or unsubstituted alkyl, amino, amidino, guanidino, heterocyclic, or aryl, wherein said substituents are amino, arylalkyl, aminoalkyl, alkyl, aryl, alkenyl, or alkynyl; and

A is a substituted or unsubstituted phenyl, heteroaryl, cycloalkyl, or biaryl, and pharmaceutically acceptable salts thereof.

127. The pharmaceutical composition of claim 124-126, wherein said MC4-R binding compound is an MC4-R antagonist.

128. The pharmaceutical composition of any one of claims 124-127, wherein said MC4-R associated state is associated with pigmentation.

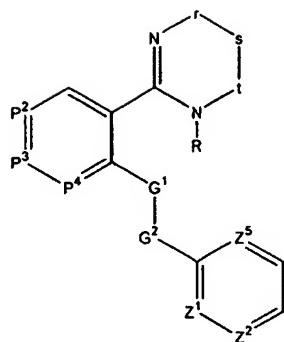
20 129. The pharmaceutical composition of any one of claims 124-127, wherein said MC4-R associated state is associated with weight loss.

130. The pharmaceutical composition of claim 129, wherein said weight loss is a result of old age, anorexia nervosa, HIV cachexia or cancer cachexia.

25

131. The pharmaceutical composition of any one of claims 124-130, wherein said mammal is a human.

30 132. The pharmaceutical composition of any one of claims 124-131, wherein said MC4-R binding compound is of the formula (IX):



(IX)

wherein:

- P² is CH, CF, CCl, CBr, C-alkyl, C-alkoxy, C-CN, or Cl;
- P³ is CH, CF, CCl, CBr, C-alkyl, C-alkoxy, C-CN, or Cl;
- 5 P⁴ is CH, CCl, CBr, CF, C-alkyl, C-alkoxy, C-CN, or Cl;
- G¹ and G² are each independently CH₂, S, or O;
- r is a covalent bond or CH₂;
- t is CH₂, CR³, or CR³R⁴;
- s is CH₂, CHR⁵ or CR⁵R⁶;
- 10 R is hydrogen or alkyl;
- Z¹ is CH, or covalently linked to Z² to form a naphthyl ring;
- Z² is CH, C-(C≡CH), CCl, CBr, CI, CF, or covalently linked to Z¹ to form a naphthyl ring;
- Z⁵ is CH, or C-OMe;
- 15 R³, R⁴, R⁵, and R⁶ are methyl or ethyl, or pharmaceutically acceptable salts thereof.

133. The pharmaceutical composition of claim 133, wherein said MC4-R binding compound is selected from the group consisting of: 2-[2-(4-benzyloxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 20 2-[2-(2-iodo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-methoxy-5-nitro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(3-chloro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 25 2-[2-(2,5-dimethoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(3-bromo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;

- 2-[2-(2-iodo-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
2-[2-(2-methoxy-5-nitro-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
2-[2-(2-methoxy-5-nitro-benzyloxy)-phenyl]-1,4,5,6-tetrahydropyrimidine;
2-[2-(2-bromo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 5 2-[2-(3-iodo-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-methoxy-5-nitro-benzylsulfanyl)-phenyl]-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazole;
2-{2-[2-(2-methoxy-naphthalen-1-yl)-ethyl]-phenyl}-1,4,5,6-tetrahydropyrimidine;
2-[2-(5-bromo-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6,-tetrahydropyrimidine;
- 10 10 2-{2-[2-(2-methyl-naphthalen-1-yl)-ethyl]-phenyl}-1,4,5,6-tetrahydropyrimidine;
2-{2-[2-(2,3-dihydro-benzo[1,4]dioxin-5-yl) -ethyl]-phenyl}-1,4,5,6-tetrahydropyrimidine;
2-[2-(2-methoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydropyrimidine;
2-(2-Benzylsulfanyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine;
- 15 15 2-(2-Pentadecylsulfanyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine;
2-(2-Cyclohexylmethylsulfanyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Methyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(3-Nitro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(3,5-Dimethoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 20 20 2-[2-(4-Fluoro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Chloro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Fluoro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2,4-Bis-trifluoromethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(3-Methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 25 25 2-[2-(3,5-Bis-trifluoromethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Methoxy-5-nitro-benzyloxy)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
2-(2-Benzylsulfanyl-phenyl)-4,5-dihydro-1H-imidazole;
2-[2-(2,6-Difluoro-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 30 30 2-[2-(Naphthalen-1-ylmethoxy)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
1-{2-[2-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-5,6-dihydro-4H-pyrimidin-1-yl}-ethanone;

- 2-[2-(2-Chloro-6-fluoro-benzylsulfanyl)-phenyl]-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazole;
- 2-[2-(2-Iodo-benzylsulfanyl)-phenyl]-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazole;
- 2-[2-(2,5-Dimethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 5 4-[2-(1,4,5,6-Tetrahydro-pyrimidin-2-yl)-phenylsulfanyl]methyl]-quinoline;
- 2-[2-(2-Methoxy-5-nitro-benzylsulfanyl)-pyridin-3-yl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Cyclopentyloxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2,3-Dihydro-benzo[1,4]dioxin-5-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
- 10 pyrimidine;
- 2-[2-(6-Methoxy-2,3-dihydro-benzo[1,4]dioxin-5-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-fluoro-2-methoxy-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
- 1-Methyl-2-[2-(naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 15 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
- 2-[2-(5-Bromo-2-methoxy-benzyloxy)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(Naphthalen-1-yloxymethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-5,5-dimethyl-1,4,5,6-tetrahydro-
- pyrimidine;
- 20 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-5,5-dimethyl-4,5-dihydro-1H-imidazole;
- 2-[2-(2,6-Dimethoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Bromo-6-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[5-Bromo-2-(5-bromo-2-methoxy-benzylsulfanyl)-phenyl]-4,5-dihydro-1H-imidazole;
- 25 2-[5-Bromo-2-(5-bromo-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[4-Bromo-2-(5-bromo-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Bromo-5-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 30 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-5-methyl-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(Biphenyl-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Chloro-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;

- 2-[2-(2-Methoxy-5-thiophen-3-yl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(Biphenyl-2-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Iodo-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 5 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-5-fluoro-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(4,4'-Dimethoxy-biphenyl-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 10 2-[2-(9H-Fluoren-9-ylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(3'-Chloro-4'-fluoro-4-methoxy-biphenyl-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(1-Naphthalen-1-yl-ethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 15 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-5-fluoro-phenyl]-4,5-dihydro-1H-imidazole;
- 2-(2-Benzhydrylsulfanyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2'-Fluoro-4"-methoxy-[1,1';4',1"]terphenyl-3"-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzamidine;
- 20 2-[4-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Ethynyl-2-methoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-cyclopentyloxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 25 2-[2-(5-Bromo-2-ethoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-propoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- [2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-diethyl-amine;
- 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-piperazine;
- C-{4-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-quinoxalin-2-yl]-morpholin-2-yl}-
- 30 methylamine;
- 2-[2-(2-Methoxy-5-methyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylloxymethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- [2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-dimethyl-amine;

- 2-[2-(5-Bromo-2-isopropoxy-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Ethoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Propoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
4-Methoxy-3-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenylsulfanylmethyl]-
5 benzonitrile;
1-{4-Methoxy-3-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenylsulfanylmethyl]-phenyl}-
ethanone;
2-[2-(Naphthalen-1-ylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-piperidine;
10 C-{4-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-morpholin-2-yl}-
methylamine;
1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-pyrrolidin-3-ylamine;
1-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-pyrrolidin-3-ylamine;
3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-1,5,6,7,8,8a-hexahydro-
15 imidazo[1,5-a]pyridine;
3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-5,6,7,7a-tetrahydro-1H-
pyrrolo[1,2-c]imidazole;
2-[2-(Benzo[b]thiophen-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[3-Fluoro-2-(naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
20 2-(Naphthalen-1-ylmethylsulfanyl)-3-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenylamine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
2-[2-(2-Methoxy-phenylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
1-{2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-5,6-dihydro-4H-pyrimidin-1-yl}-
25 3-methyl-butan-1-one;
1-{2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-5,6-dihydro-4H-pyrimidin-1-yl}-
2-phenyl-ethanone;
2-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-pyridin-2-yl]-1,4,5,6-tetrahydro-pyrimidine;
N-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-guanidine;
30 2-[2-(2-Isopropoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;
2-[2-(2-Cyclopentyloxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
pyrimidine;

- (5-Bromo-2-methoxy-benzyl)-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenyl]-amine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl methyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Methoxy-naphthalen-1-ylsulfanyl methyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
5 pyrimidine;
2-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-pyrazin-2-yl]-1,4,5,6-tetrahydro-pyrimidine;
2-[3-Chloro-2-(naphthalen-1-ylsulfanyl methyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(6-Bromo-2-methoxy-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
10 2-[3-Chloro-2-(2-methoxy-naphthalen-1-ylsulfanyl methyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(5-Bromo-2-methoxy-phenylsulfanyl methyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(5-Bromo-2-methoxy-phenylsulfanyl methyl)-3-chloro-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
15 2-[1-(2-Naphthalen-1-yl-ethyl)-1H-pyrrol-2-yl]-1,4,5,6-tetrahydro-pyrimidine;
(5-Bromo-2-methoxy-benzyl)-methyl-[2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenyl]-amine;
2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzylamine;
20 2-[2-(2-Chloro-phenylsulfanyl methyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2-Bromo-phenylsulfanyl methyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-(2-o-Tolylsulfanyl methyl-phenyl)-1,4,5,6-tetrahydro-pyrimidine;
2-[2-(2,5-Dichloro-phenylsulfanyl methyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
2-(3-Amino-propylamino)-6-(5-bromo-2-methoxy-benzylsulfanyl)-benzonitrile;
25 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-1,4,5,6-tetrahydro-pyrimidine;
[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-diethyl-amine;
4-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-morpholine;
3'-(5-Bromo-2-methoxy-benzylsulfanyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl;
2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-piperazin-1-yl-6,7-dihydro-quinoxaline;
30 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-piperidine;
C-{4-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-morpholin-2-yl}-methylamine;
1-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-pyrazin-2-yl]-pyrrolidin-3-ylamine;

- 1-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-quinoxalin-2-yl]-pyrrolidin-3-ylamine;
1-[2-(2-Methoxy-naphthalen-1-ylmethylsulfanyl)-benzyl]-pyrrolidin-3-ylamine;
C-{4-[3-(5-Bromo-2-methoxy-benzylsulfanyl)-pyrazin-2-yl]-morpholin-3-yl}-methylamine;
- 5 1-[3-Fluoro-2-(2-naphthalen-1-yl-ethyl)-benzyl]-piperazine;
1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-azetidine;
1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-pyrrolidin-3-ol;
[2-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester;
- 10 [2-(2-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester;
[2-(2-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 2-piperidin-1-yl-ethyl ester;
{1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-pyrrolidin-2-yl}-methanol;
- 15 4-tert-Butyl-N-naphthalen-1-ylmethyl-N-(2-piperidin-1-yl-ethyl)-benzamide;
N,N-Dimethyl-N'-naphthalen-2-ylmethyl-N'-naphthalen-1-ylmethyl-propane-1,3-diamine;
N-(5-Bromo-2-methoxy-benzyl)-N',N'-dimethyl-N-naphthalen-1-ylmethyl-propane-1,3-diamine;
- 20 1-Naphthalen-1-ylmethyl-3-phenethyl-1-(2-piperidin-1-yl-ethyl)-thiourea;
3-(4-Dimethylamino-phenyl)-1-(3-dimethylamino-propyl)-1-naphthalen-1-ylmethyl-thiourea;
4-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzylamino]-piperidine-1-
- 25 carboxylic acid ethyl ester;
2-[2-(2-Naphthalen-1-yl-ethyl)-phenyl]-ethylamine;
Naphthalene-2-sulfonic acid (2-dimethylamino-ethyl)-naphthalen-1-ylmethyl-amide;
1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-2-methoxymethyl-pyrrolidine;
- 30 (2-Hexyloxy-phenyl)-carbamic acid 2-piperidin-1-yl-1-piperidin-1-ylmethyl-ethyl ester;
3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyloxy]-pyrrolidine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyloxymethyl]-pyrrolidine;
2-[2-(Naphthalen-1-ylsulfanylmethyl)-phenyl]-piperidine;

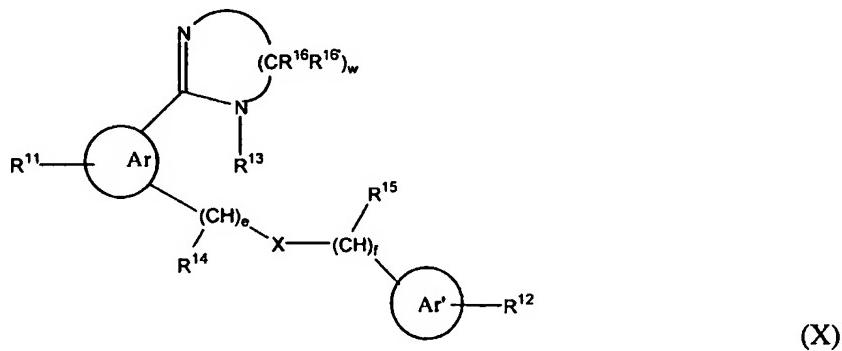
- 3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzylamino]-propan-1-ol;
3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzylamino]-3-methyl-butan-1-ol;
1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-pyrrolidin-3-ol;
{1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-pyrrolidin-2-yl}-methanol;
- 5 {1-[2-(Naphthalen-1-ylsulfanyl)methyl]-benzyl]-piperidin-2-yl}-methanol;
2-[2-(Naphthalen-1-ylsulfanyl)methyl]-pyrrolidin-1-yl]-ethyl-N-pyrrolidine;
N-pyrrolyl-[1-(2-naphthalen-1-yl-ethyl)-pyrrolidin-2-ylmethyl]-amine;
1-(2-Naphthalen-1-yl-ethyl)-piperidine-2-carboxylic acid methyl ester;
(3-Bromo-benzyl)-(1-ethyl-pyrrolidin-2-ylmethyl)-naphthalen-1-ylmethyl-amine;
- 10 3-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyloxy]-piperidine;
(5-Bromo-2-methoxy-benzyl)-(1-ethyl-pyrrolidin-2-ylmethyl)-naphthalen-1-ylmethyl-amine;
(1-Ethyl-pyrrolidin-2-ylmethyl)-naphthalen-2-ylmethyl-naphthalen-1-ylmethyl-amine;
2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyloxymethyl]-pyrrolidine;
- 15 (3-Bromo-benzyl)-(3-imidazol-1-yl-propyl)-naphthalen-1-ylmethyl-amine;
(3-Imidazol-1-yl-propyl)-naphthalen-2-ylmethyl-naphthalen-1-ylmethyl-amine;
[2-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 2-piperidin-1-yl-1-piperidin-1-ylmethyl-ethyl ester;
[2-(Naphthalen-1-ylmethylsulfanyl)-phenyl]-carbamic acid 2-dimethylamino-ethyl ester;
- 20 1-[2-(Naphthalen-1-ylsulfanyl)methyl]-benzyl]-piperazine;
[3-(2-Methyl-piperidin-1-yl)-propyl]-[2-(naphthalen-1-ylsulfanyl)methyl]-benzyl]-amine;
1-[3-Chloro-2-(naphthalen-1-ylsulfanyl)methyl]-benzyl]-piperazine;
N,N-Dimethyl-N'-(2-naphthalen-1-yl-ethyl)-N'-naphthalen-1-ylmethyl-ethane-1,2-
- 25 diamine;
{1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-piperidin-2-yl}-methanol;
1-[2-(2-Naphthalen-1-yl-ethyl)-benzyl]-piperazine;
[3-(2-Methyl-piperidin-1-yl)-propyl]-[2-(2-naphthalen-1-yl-ethyl)-benzyl]-amine;
1-[3-Fluoro-2-(2-naphthalen-1-yl-ethyl)-benzyl]-piperazine;
- 30 {1-[3-Chloro-2-(naphthalen-1-ylsulfanyl)methyl]-benzyl]-piperidin-2-yl}-methanol;
{1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-piperidin-2-yl}-methanol;
{1-[2-(2-Naphthalen-1-yl-ethyl)-benzyl]-piperidin-2-yl}-methanol;
[3-(2-Methyl-piperidin-1-yl)-propyl]-[2-(2-naphthalen-1-yl-ethyl)-benzyl]-amine;

- 1-[2-(2-Naphthalen-1-yl-ethyl)-benzyl]-pyrrolidin-3-ylamine;
- 1-Phenyl-3-piperazin-1-yl-5,6,7,8-tetrahydro-isoquinoline-4-carbonitrile;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-6-ethyl-1,4,5,6-tetrahydro-pyrimidine;
- 5 2-[2-(4-Methoxy-biphenyl-3-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Methoxy-5-phenylethynyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Naphthalen-1-yl-ethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 10 2-[3-(2-Methoxy-naphthalen-1-ylsulfanylmethyl)-thiophen-2-yl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2,5-Dimethoxy-phenylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(4-Methyl-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-4,4-dimethyl-4,5-dihydro-1H-imidazole;
- 15 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-5,5-dimethyl-1,4,5,6-tetrahydro-pyrimidine;
- 2-[3-(Naphthalen-1-ylsulfanylmethyl)-thiophen-2-yl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-phenyl}-1,4,5,6-tetrahydro-pyrimidine;
- 2-[3-Chloro-2-(2-naphthalen-1-yl-ethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 20 2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-3-fluoro-phenyl}-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-phenylsulfanylmethyl)-3-fluoro-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(Naphthalen-1-ylsulfanylmethyl)-phenyl]-4,5-dihydro-1H-imidazole;
- 25 2-[3-Fluoro-2-(naphthalen-1-ylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[3-Bromo-2-(naphthalen-1-ylsulfanylmethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-3-chloro-phenyl}-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Methoxy-5-trifluoromethyl-benzylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-
- 30 pyrimidine;
- 2-[4-(Naphthalen-1-ylsulfanylmethyl)-thiophen-3-yl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(Naphthalen-1-ylsulfanylmethyl)-thiophen-3-yl]-1,4,5,6-tetrahydro-pyrimidine;

- 2-[2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-3-trifluoromethyl-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(2-Naphthalen-1-yl-ethyl)-3-trifluoromethyl-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(6-Fluoro-naphthalen-1-ylmethylsulfanyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 5 {1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-benzyl]-piperidin-2-yl}-methanol;
- 2-[3-Fluoro-2-(2-naphthalen-1-yl-ethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- [2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-[3-(2-methyl-piperidin-1-yl)-propyl]-amine;
- 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-pyrrolidin-3-ylamine;
- 10 1-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-benzyl]-piperazine;
- 5,5-Dimethyl-2-[2-(2-naphthalen-1-yl-ethyl)-phenyl]-4,5-dihydro-1H-imidazole;
- 2-[3-Fluoro-2-(2-naphthalen-1-yl-ethyl)-phenyl]-5,5-dimethyl-4,5-dihydro-1H-imidazole;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3,5-difluoro-phenyl]-1,4,5,6-tetrahydro-
- 15 pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3,5-difluoro-phenyl]-5,5-dimethyl-4,5-dihydro-1H-imidazole;
- 3-(2-Naphthalen-1-yl-ethyl)-2-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-phenylamine;
- Amino-[2-(2-naphthalen-1-yl-ethyl)-phenyl]-acetonitrile;
- 20 1-[2-(2-Naphthalen-1-yl-ethyl)-phenyl]-ethane-1,2-diamine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-4-methyl-4,5-dihydro-1H-imidazole;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-fluoro-phenyl]-4-methyl-4,5-dihydro-1H-imidazole;
- 25 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-phenyl]-4-methyl-4,5-dihydro-1H-imidazole;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3,4-difluoro-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[3-Fluoro-2-(naphthalen-1-ylsulfanylmethyl)-phenyl]-5,5-dimethyl-4,5-dihydro-1H-
- 30 imidazole;
- 2-{2-[2-(5-Bromo-2-methoxy-phenyl)-1-methyl-ethyl]-phenyl}-1,4,5,6-tetrahydro-pyrimidine;

- 2-[2-(5-Bromo-2-methoxy benzyl sulfanyl)-3-fluoro-4-trifluoromethyl-phenyl]-4,4-dimethyl-4,5-dihydro-1H-imidazole;
- 2-[2-(5-Bromo-2-methoxy-benzyl sulfanyl)-3-fluoro-4-trifluoromethyl-phenyl]-5,5-dimethyl-1,4,5,6-tetrahydro-pyrimidine;
- 5 2-[3-Methoxy-2-(2-naphthalen-1-yl-ethyl)-phenyl]-1,4,5,6-tetrahydro-pyrimidine;
- 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-3-chloro-phenyl]-1,4,5,6-tetrahydro-pyrimidin-5-ol;
- 2-{2-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-3-methoxy-phenyl}-1,4,5,6-tetrahydro-pyrimidine;
- 10 2-[2-(5-Bromo-2-methoxy-benzylsulfanyl)-phenyl]-6-ethyl-1,4,5,6-tetrahydro-pyrimidine, and pharmaceutically acceptable salts thereof.
132. The pharmaceutical composition of any one of claims 124-131, wherein said MC4-R binding compound is not 10-[2-(1-methyl-piperadin-2-yl)-ethyl]-2-methylsulfanyl-10H-phenothiazine.
- 15 133. The pharmaceutical composition of any one of claims 124-131, wherein said MC4-R binding compound is not 2-naphthalen-1-ylmethyl-4,5-dihydro-1H-imidazole.
- 20 134. The pharmaceutical composition of any one of claims 124-131, wherein said MC4-R binding compound is not (2,6-dichloro-phenyl)-imidazolidin-2-ylidene-amine.
135. The pharmaceutical composition of any one of claims 124-131, wherein said MC4-R binding compound is not 2-benzyl-4,5-dihydro-1H-imidazole.
- 25 136. The pharmaceutical composition of any one of claims 124-131, wherein said MC4-R binding compound is not 5-(4-chloro-phenyl)-2,5-dihydro-3H-imidazo[2,1-a]-isoindol-5-ol.
- 30 137. The pharmaceutical composition of claim 124-136, wherein said pharmaceutical composition is suitable for oral administration.

138. A method for treating an MC4-R associated state in a mammal comprising administering an effective amount of a MC4-R binding compound to a mammal such that the MC4-R associated state is treated, wherein said compound is of the formula (X):



5 wherein

Ar and Ar' are aromatic groups;

- R¹¹ is selected independently for each position capable of substitution from the group hydrogen, cyano, halogen, alkyl, amino, or aryloxy;
- R¹² is selected for each position capable of substitution from the group consisting of hydrogen, halogen, alkoxy, acetylenic, nitro, aryl, alkyl, alkenyl, alkynyl, cyano, acyl, or carbonyl;

R¹³ is hydrogen, alkenyl, alkynyl, aralkyl, nitro, cyano, alkyl, acyl, carbonyl, or SO₂CH₃, and may optionally be linked to an R¹⁶ or an R¹⁶' group;

- R¹⁶ and R¹⁶' are each independently selected for each position capable of substitution from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heterocyclic, carbonyl, or acyl, and may optionally be connected through an alkyl chain to R¹³ or another R¹⁶ or R¹⁶' group, to form a fused or spiro ring system;

X is NR¹⁷, S, O or a covalent bond;

R¹⁷ is hydrogen, alkyl, alkenyl, alkynyl, acyl, heterocyclic, or carbonyl;

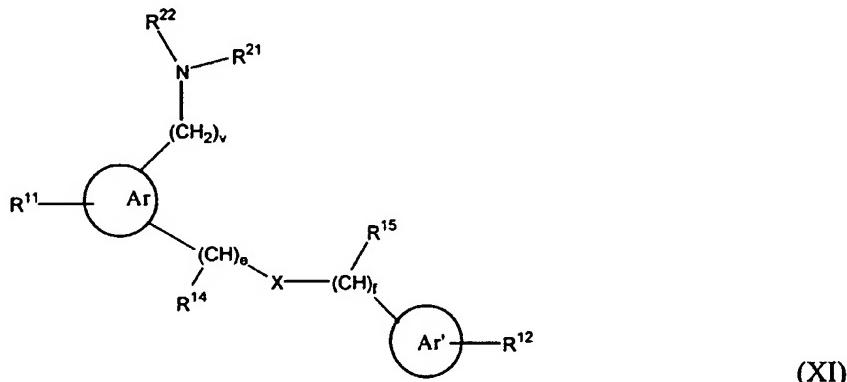
- R¹⁴ and R¹⁵ are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, heteroaromatic, halogen, nitro, cyano, amino, or aryl, for each occurrence;

w is 0, 1, 2, 3, or 4;

e is 0, 1, 2, or 3;

- f is 0, 1, 2, or 3, and pharmaceutically acceptable salts thereof.

139. A method for treating an MC4-R associated state in a mammal comprising administering an effective amount of a MC4-R binding compound to a mammal such that the MC4-R associated state is treated, wherein said compound is of the formula (XI):



5

wherein

Ar and Ar' are aromatic groups, as described above;

R¹¹ is selected independently for each position capable of substitution from the group hydrogen, halogen, alkyl, amino, cyano, or aryloxy.

10 R¹² is selected for each position capable of substitution from the group consisting of hydrogen, halogen, alkoxy, acetylenic, nitro, aryl, alkyl, alkenyl, alkynyl, cyano, acyl, or carbonyl;

X is NR¹⁷, S, O or a covalent bond;

R¹⁷ is hydrogen, alkyl, acyl, heterocyclic, or carbonyl;

15 R¹⁴ and R¹⁵ are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, or aryl, for each occurrence;

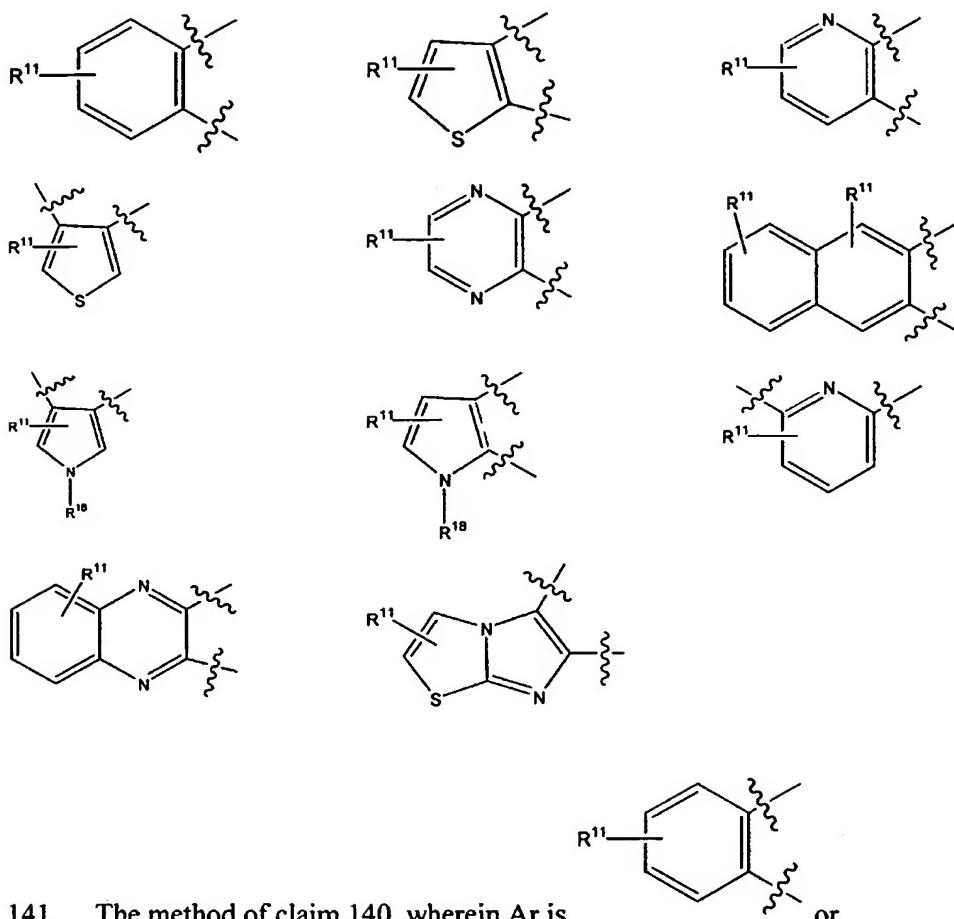
R²⁰ and R²¹ are each independently selected from the group consisting of substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, hydrogen, or carbonyl, and may optionally be linked to form a heterocycle;

20 v is 0, 1, 2, 3, 4, 5, or 6;

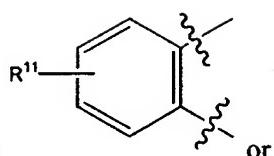
e is 0, 1, 2, or 3;

f is 0, 1, 2, or 3, and pharmaceutically acceptable salts thereof.

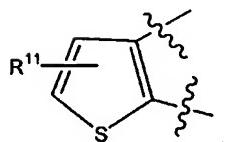
140. The method according to claim 138 or 139, wherein Ar is selected from the
25 group consisting of:



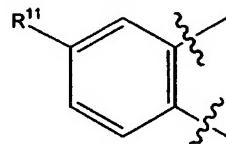
141. The method of claim 140, wherein Ar is



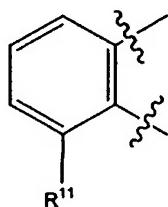
or



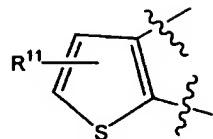
5 142. The method of claim 141, wherein Ar is:



143. The method of claim 141, wherein Ar is:



144. The method of claim 141, wherein Ar is



5 145. The method of claim 138-144, wherein R¹¹ is selected independently for each aromatic position capable of substitution from the group consisting of hydrogen, halogen, alkyl, amino, and benzyloxy.

10 146. The method according to claim 145, wherein each R¹¹ is independently hydrogen or halogen.

147. The method according to claim 146, wherein said halogen is fluorine, chlorine, or bromine.

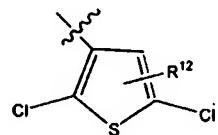
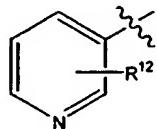
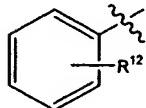
15 148. The method according to claim 147, wherein said halogen is fluorine.

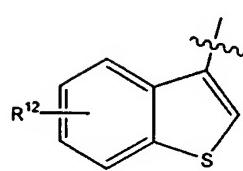
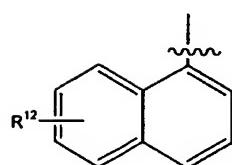
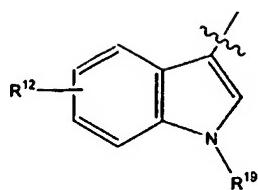
149. The method according to claim 147, wherein said halogen is chlorine.

150. The method according to claim 147, wherein said halogen is bromine.
20

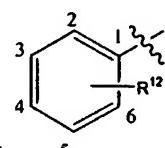
151. The method according to claim 146, wherein each R¹¹ is hydrogen.

152. The method according to claim 138-151, wherein Ar' is selected from the group consisting of:

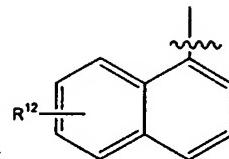




wherein R¹⁹ is hydrogen, alkyl, acyl, aryl, alkenyl, or alkynyl.



153. The method of claim 152, wherein Ar' is



5 154. The method of claim 152, wherein Ar' is

155. The method of claim 153, wherein R¹² is in the 3 position.

156. The method of claim 153, wherein R¹² is in the 6 position.

10

157. The method according to claims 138-156, wherein each R¹² is selected independently for each aromatic position capable of being substituted from the group consisting of hydrogen, alkoxy, halogen, or cyano.

15 158. The method according to claim 157, wherein each R¹² is hydrogen, halogen, or alkoxy.

159. The method according to claim 158, wherein said alkoxy is C₁-C₁₀ alkoxy.

20 160. The method according to claim 159, wherein said C₁-C₁₀ alkoxy is selected from the group consisting of methoxy, ethoxy, n-propoxy, i-propoxy, and cyclopentoxy.

161. The method according to claim 160, wherein said C₁-C₁₀ alkoxy is methoxy.

162. The method according to claim 158, wherein said halogen is bromine, fluorine, iodine or chlorine.
- 5 163. The method according to claim 162, wherein said halogen is bromine.
164. The method according to claim 162, wherein said halogen is fluorine.
165. The method according to claim 162, wherein said halogen is chlorine.
- 10 166. The method according to any one of claims 138-165 wherein X is a covalent bond.
167. The method according to any one of claims 138-165 wherein X is S.
- 15 168. The method according to any one of claims 138 -165 wherein X is O.
169. The method according to any one of claims 138-165 wherein X is NR¹⁷.
- 20 170. The method of claim 169, wherein R¹⁷ is hydrogen, alkyl, or acyl.
171. The method of claim 170, wherein said alkyl is C₁-C₁₀ alkyl.
172. The method of claim 171, wherein said alkyl is methyl.
- 25 173. The method of claim 170, wherein R¹⁷ is hydrogen.
174. The method of any one of claims 138, or 140-173, wherein R¹⁶ and R^{16'} are independently selected for each position from the group consisting of hydrogen and
- 30 alkyl.
175. The method of claim 174, wherein at least one of R¹⁶ and R^{16'} is hydrogen.

176. The method of claim 174, wherein at least one of R¹⁶ and R^{16'} is at least once C₁-C₁₀ alkyl.

5 177. The method of claim 176, wherein said C₁-C₁₀ alkyl is methyl.

178. The method of claim 176, wherein said C₁-C₁₀ alkyl is ethyl.

179. The method of any one of claims 138, or 140-173, wherein at least two of the R¹⁶
10 and R^{16'} are linked to form a ring.

180. The method of any one of claims 138-179, wherein R¹⁴ and R¹⁵ are each
independently selected from the group consisting of hydrogen, alkyl and phenyl for each
occurrence.

15

181. The method of claim 180, wherein R¹⁴ and R¹⁵ are hydrogen for each occurrence.

182. The method of claim 180 wherein said alkyl is C₁-C₁₀.

20 183. The method of claim 182, wherein said alkyl is methyl.

184. The method of any one of claims 138, or 140-183, wherein said R¹³ group is
hydrogen, acyl, alkyl, acyl, carboxy, or SO₂CH₃.

25 185. The method of claim 184, wherein R¹³ is hydrogen.

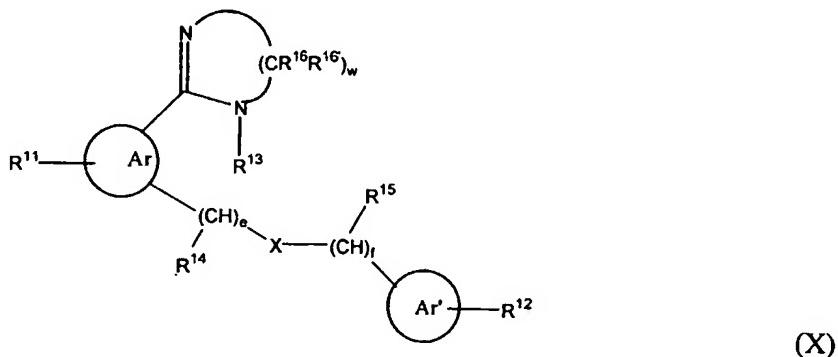
186. The method of claim 184, wherein said R¹³ group is optionally substituted C₁-C₁₀ alkyl or acyl.

30 187. The method of claim 186, wherein said acyl group is i-propylcarbonyl,
benzylcarbonyl.

188. The method of claim 186, wherein said alkyl group is C₁-C₁₀ alkyl.

189. The method of claim 188, wherein said alkyl group is methyl.
190. The method of any one of claims 138, or 140-189, wherein w is 2.
5
191. The method of any one of claims 138, or 140-189, wherein w is 3.
192. The method of any one of claims 138-191, wherein e is 0.
- 10 193. The method of any one of claims 138-191, wherein e is 1.
194. The method of any one of claims 138-193, wherein f is 0.
195. The method of any one of claims 138-193, wherein f is 1.
15
196. The method of any one of claims 138-193 wherein f is 2.
197. The method of any one of claims 139-173, wherein R²⁰ and R²¹ are each independently selected from the group consisting of substituted or unsubstituted alkyl, carbonyl, and may optionally be linked to form a heterocycle.
20
198. The method of claim 197, wherein said heterocycle is piperazinyl or morpholinyl.
- 25 199. The method of any one of claims 139-173, 197 or 198, wherein v is 1, 2, or 3.
200. The method of any one of claims 1-113 or 138-199, wherein the MC4-R associated state is not weight loss.
- 30 201. A pharmaceutical composition for the treatment of an MC4-R associated state in a mammal comprising a pharmaceutically acceptable carrier and an MC4-R binding compound such as those shown in any one of the methods claims 1-113 or 138-199.

202. A pharmaceutical composition for the treatment of a MC4-R associated state in a mammal comprising a pharmaceutically acceptable carrier and an effective amount of an MC4-R binding compound of the formula (X):



5 wherein

Ar and Ar' are aromatic groups;

R¹¹ is selected independently for each position capable of substitution from the group hydrogen, cyano, halogen, alkyl, amino, or aryloxy;

10 R¹² is selected for each position capable of substitution from the group consisting of hydrogen, halogen, alkoxy, acetylenic, nitro, aryl, alkyl, alkenyl, alkynyl, cyano, acyl, or carbonyl;

R¹³ is hydrogen, alkenyl, alkynyl, aralkyl, nitro, cyano, alkyl, acyl, carbonyl, or SO₂CH₃, and may optionally be linked to an R¹⁶ or an R¹⁶' group;

15 R¹⁶ and R¹⁶' are each independently selected for each position capable of substitution from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heterocyclic, carbonyl, or acyl, and may optionally be connected through an alkyl chain to R¹³ or another R¹⁶ or R¹⁶' group, to form a fused or spiro ring system;

X is NR¹⁷, S, O or a covalent bond;

R¹⁷ is hydrogen, alkyl, alkenyl, alkynyl, acyl, heterocyclic, or carbonyl;

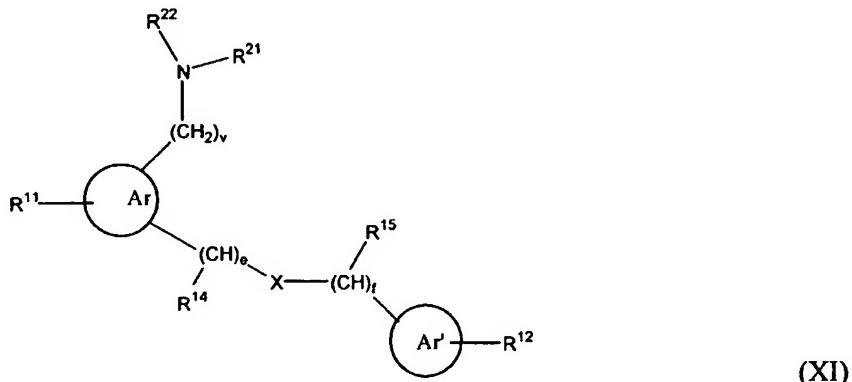
20 R¹⁴ and R¹⁵ are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, heteroaromatic, halogen, nitro, cyano, amino, or aryl, for each occurrence;

w is 0, 1, 2, 3, or 4;

e is 0, 1, 2, or 3;

25 f is 0, 1, 2, or 3, and pharmaceutically acceptable salts thereof.

203. A pharmaceutical composition for the treatment of a MC4-R associated state in a mammal comprising a pharmaceutically acceptable carrier and an effective amount of an MC4-R binding compound of the formula (XI):



5 wherein

Ar and Ar' are aromatic groups, as described above;

R¹¹ is selected independently for each position capable of substitution from the group hydrogen, halogen, alkyl, amino, cyano, or aryloxy.

10 R¹² is selected for each position capable of substitution from the group consisting of hydrogen, halogen, alkoxy, acetylenic, nitro, aryl, alkyl, alkenyl, alkynyl, cyano, acyl, or carbonyl;

X is NR¹⁷, S, O or a covalent bond;

R¹⁷ is hydrogen, alkyl, acyl, heterocyclic, or carbonyl;

15 R¹⁴ and R¹⁵ are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, or aryl, for each occurrence;

R²⁰ and R²¹ are each independently selected from the group consisting of substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, hydrogen, or carbonyl, and may optionally be linked to form a heterocycle;

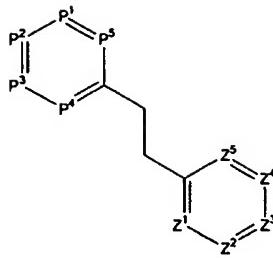
v is 0, 1, 2, 3, 4, 5, or 6;

20 e is 0, 1, 2, or 3;

f is 0, 1, 2, or 3, and pharmaceutically acceptable salts thereof.

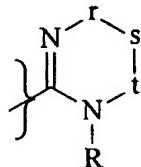
204. The MC4-R binding compound of the formula (VII):

-206-



(VII)

wherein

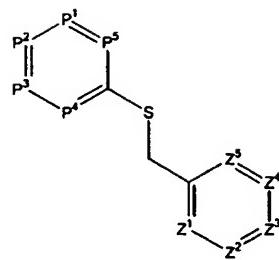
 Z^1, Z^2, Z^3, Z^4 , and Z^5 are CH, N, or substituted carbon; P^1, P^2, P^3 , and P^4 are CH, N or substituted carbon; and5 P^5 is C-J, wherein J is a moiety of the formula (XIII):

(XIII)

wherein

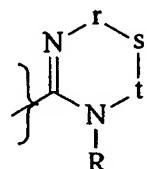
r is a covalent bond, CH, CH₂, CR¹, CR¹R², or H;t is CH, CH₂, CR³, CR³R⁴, or H;10 s is CH, CH₂, CHR⁵, CR⁵R⁶, or absent;R is hydrogen, alkyl, alkenyl, arylalkyl, benzocarbonyl, arylalkylcarbonyl, alkylcarbonyl, optionally linked to R¹, R², R³, R⁴, R⁵, or R⁶ to form one or more rings; andR¹, R², R³, R⁴, R⁵, and R⁶ are each halogen, thiol, alkoxy, alkyl, alkenyl,15 alkynyl, heterocyclic, hydroxyl, nitro, amino, cyano, aryl, optionally linked to form a ring with R, R¹, R², R³, R⁴, R⁵, or R⁶.

205. The MC4-R binding compound of the formula (VIII):



(VIII)

wherein

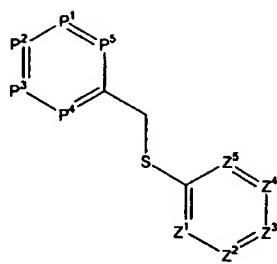
 Z^1, Z^2, Z^3, Z^4 , and Z^5 are CH, N, or substituted carbon; P^1, P^2, P^3 , and P^4 are CH, N or substituted carbon; and5 P^5 is C-J, wherein J is a moiety of the formula (XIII):

(XIII)

wherein

r is a covalent bond, CH, CH₂, CR¹, CR¹R², or H;t is CH, CH₂, CR³, CR³R⁴, or H;10 s is CH, CH₂, CHR⁵, CR⁵R⁶, or absent;R is hydrogen, alkyl, alkenyl, arylalkyl, benzocarbonyl, arylalkylcarbonyl, alkylcarbonyl, optionally linked to R¹, R², R³, R⁴, R⁵, or R⁶ to form one or more rings; and15 R¹, R², R³, R⁴, R⁵, and R⁶ are each halogen, thiol, alkoxy, alkyl, alkenyl, alkynyl, heterocyclic, hydroxyl, nitro, amino, cyano, aryl, optionally linked to form a ring with R, R¹, R², R³, R⁴, R⁵, or R⁶.

206. The MC4-R binding compound of the formula (XV):

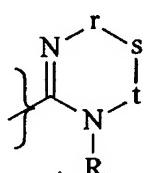


wherein

Z^1, Z^2, Z^3, Z^4 , and Z^5 are CH, N, or substituted carbon;

P^1, P^2, P^3 , and P^4 are CH, N or substituted carbon; and

5 P^5 is C-J, wherein J is a moiety of the formula (XIII):



(XIII)

wherein

r is a covalent bond, CH, CH_2 , CR^1 , CR^1R^2 , or H;

t is CH, CH_2 , CR^3 , CR^3R^4 , or H;

10 s is CH, CH_2 , CHR^5 , CR^5R^6 , or absent;

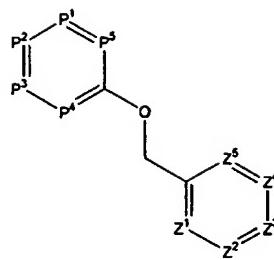
R is hydrogen, alkyl, alkenyl, arylalkyl, benzocarbonyl,

arylalkylcarbonyl, alkylcarbonyl, optionally linked to R^1, R^2, R^3, R^4, R^5 , or R^6 to form one or more rings; and

R^1, R^2, R^3, R^4, R^5 , and R^6 are each halogen, thiol, alkoxy, alkyl, alkenyl,

15 alkynyl, heterocyclic, hydroxyl, nitro, amino, cyano, aryl, optionally linked to form a ring with $R, R^1, R^2, R^3, R^4, R^5$, or R^6 .

207. The MC4-R binding compound of the formula (XVI):

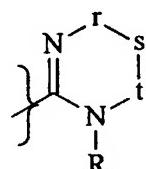


wherein

Z^1, Z^2, Z^3, Z^4 , and Z^5 are CH, N, or substituted carbon;

P^1, P^2, P^3 , and P^4 are CH, N or substituted carbon; and

5 P^5 is C-J, wherein J is a moiety of the formula (XIII):



(XIII)

wherein

r is a covalent bond, CH, CH_2 , CR^1 , CR^1R^2 , or H;

t is CH, CH_2 , CR^3 , CR^3R^4 , or H;

10 s is CH, CH_2 , CHR^5 , CR^5R^6 , or absent;

R is hydrogen, alkyl, alkenyl, arylalkyl, benzocarbonyl,

arylalkylcarbonyl, alkylcarbonyl, optionally linked to R^1, R^2, R^3, R^4, R^5 , or R^6 to form one or more rings; and

R^1, R^2, R^3, R^4, R^5 , and R^6 are each halogen, thiol, alkoxy, alkyl, alkenyl,

15 alkynyl, heterocyclic, hydroxyl, nitro, amino, cyano, aryl, optionally linked to form a ring with $R, R^1, R^2, R^3, R^4, R^5$, or R^6 .

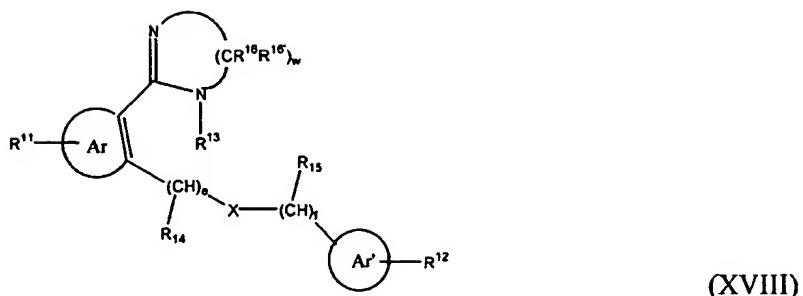
208. The compound of any one of claims 204-207, wherein P^1, P^2, P^3 , and P^4 are each substituted or unsubstituted carbon.

20

209. The compound of claim 208, wherein P^1 is CH.

210. The compound of claims 204-207, wherein at least one of P^2, P^3 and P^4 is substituted carbon.

211. The compound of any one of claims 204-207, wherein P², P³ and P⁴ are selected from the group consisting of CH, CF, Cl, CBr, C-alkyl, C-alkyoxy, or Cl.
- 5 212. The compound of any one of claims 204-207, wherein Z³ and Z⁴ are each CH.
213. The compound of any one of claims 204-207, wherein Z¹ is CH.
- 10 214. The compound of any one of claims 204-207, wherein Z¹ is covalently linked to Z² to form a naphthyl ring.
215. The compound of any one of claims 204-207, wherein Z² is CH, C-(C≡CH), CCl, CBr, Cl, and CF.
- 15 216. The compound of any one of claims 204-207, wherein L₂ is a covalent bond.
217. The compound of any one of claims 204-207, wherein R is H, alkyl, benzocarboxy, alkylcarboxy, or arylalkylcarboxy.
- 20 218. The compound of any one of claims 204-207, wherein s is CR₅R₆ and R₅ and R₆ are each methyl.
219. The compound of any one of claims 204-207, wherein r is a covalent bond.
- 25 220. The compound of any one of claims 204-207, wherein t, r and s are CH₂.
221. An MC4-R binding compound of the formula (XVIII):



wherein

- Ar and Ar' are aromatic groups;
- R¹¹ is selected independently for each position capable of substitution from the group hydrogen, cyano, alkoxy, nitro, halogen, alkyl, amino, or aryloxy;
- R¹² is selected for each position capable of substitution from the group consisting of hydrogen, halogen, alkoxy, acetylenic, nitro, aryl, alkyl, alkenyl, alkynyl, cyano, acyl, or carbonyl;
- R¹³ is hydrogen, alkenyl, alkynyl, aralkyl, nitro, cyano, alkyl, acyl, carbonyl, or SO₂CH₃, and may optionally be linked to an R¹⁶ or an R^{16'} group;
- R¹⁶ and R^{16'} are each independently selected for each position capable of substitution from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, hydroxyl, cyano, aryl, heterocyclic, carbonyl, or acyl, and may optionally be connected through an alkyl chain to R¹³ or another R¹⁶ or R^{16'} group, to form a fused or spiro ring system;
- X is NR¹⁷, S, O or a covalent bond;
- R¹⁷ is hydrogen, alkyl, or carbonyl;
- R¹⁴ and R¹⁵ are each independently hydrogen, halogen, or alkyl;
- w is 1, 2, 3, or 4;
- e is 0 or 1;
- f is 0 or 1, wherein both e and f are not both 0 if X is a covalent bond, and pharmaceutically acceptable salts thereof.

1/2

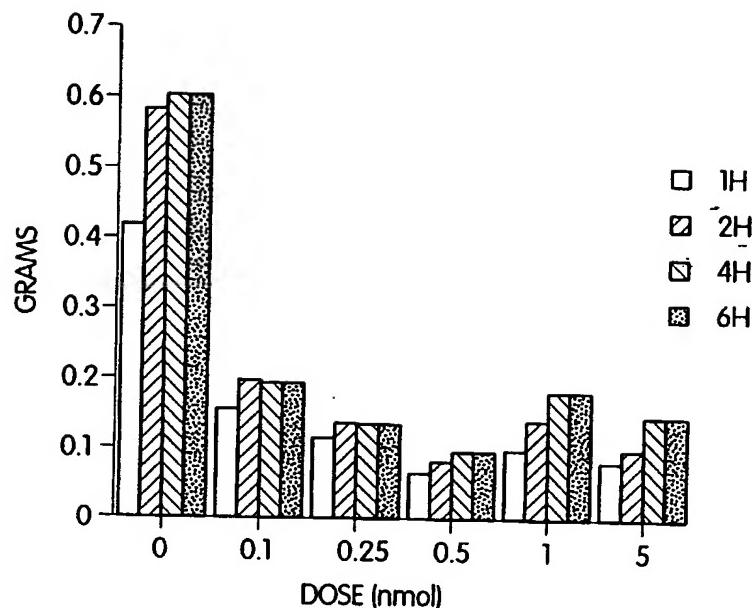


Fig. 1A

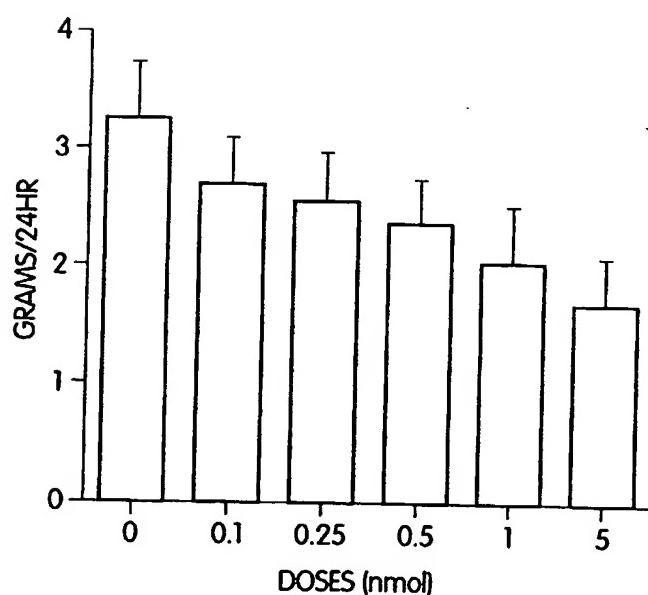


Fig. 1B

SUBSTITUTE SHEET (RULE26)

2/2

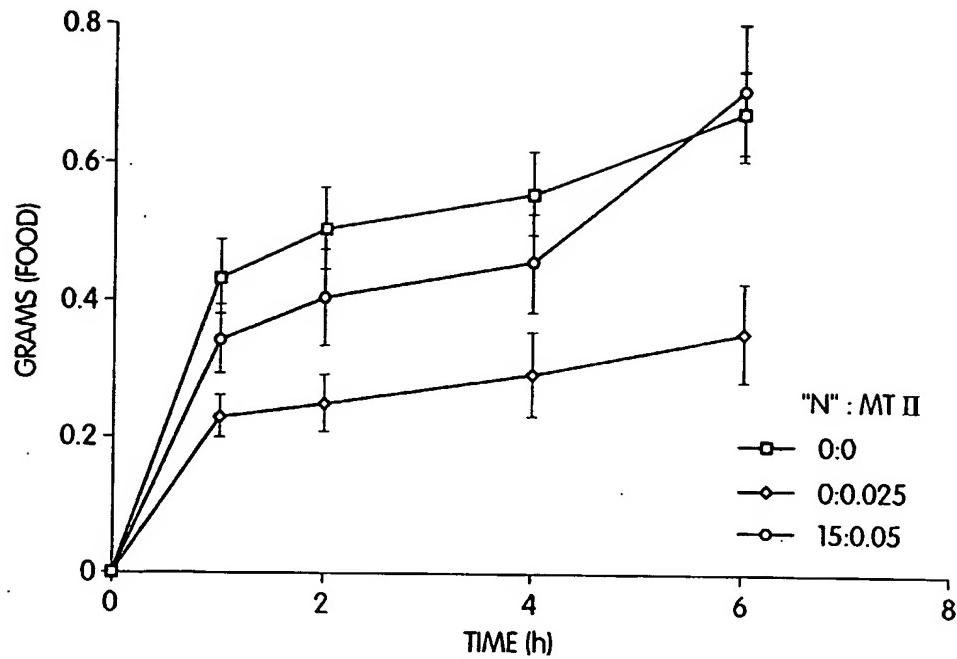


Fig. 2

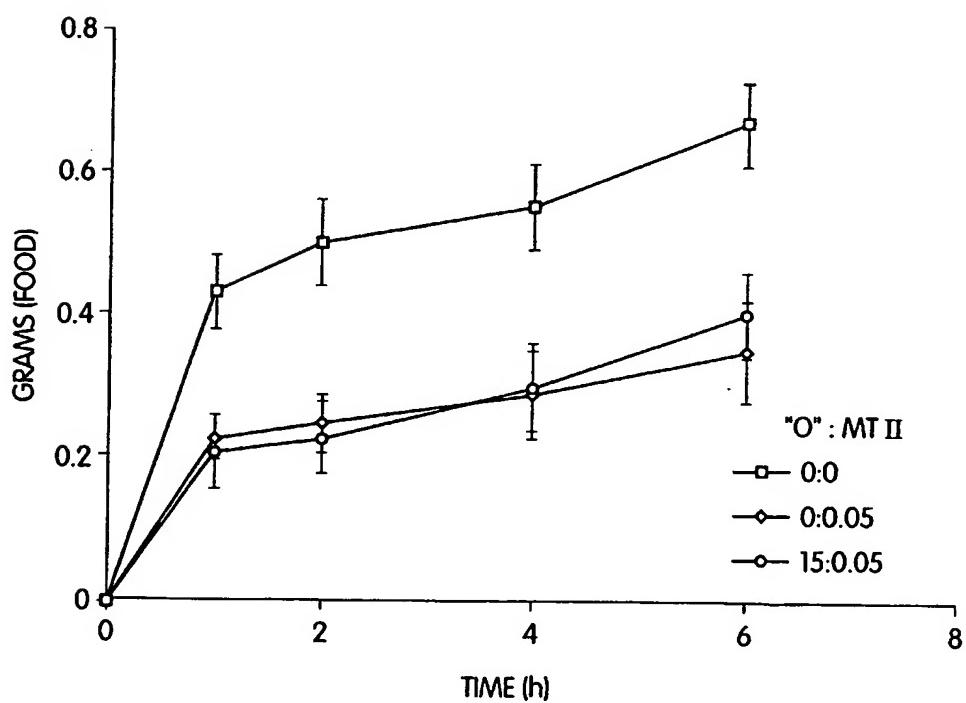


Fig. 3

SUBSTITUTE SHEET (RULE26)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
15 February 2001 (15.02.2001)

PCT

(10) International Publication Number
WO 01/10842 A3

(51) International Patent Classification⁷: **C07D 235/06**, (74) Agents: HANLEY, Elizabeth, A.; Lahive & Cockfield, LLP. 28 State Street, Boston, MA 02109 et al. (US).
239/06, 233/20, A61K 31/4184, 31/4164, 31/505, A61P 3/04

(21) International Application Number: PCT/US00/21327

(22) International Filing Date: 4 August 2000 (04.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/147,288 4 August 1999 (04.08.1999) US
60/223,277 3 August 2000 (03.08.2000) US

(71) Applicant (*for all designated States except US*): MILLENNIUM PHARMACEUTICALS, INC. [US/US]; 75 Sidney Street, Cambridge, MA 02139 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): MAGUIRE, Martin, P. [US/US]; 169 Msgr. O'Brien Hwy. Apt. #507, Cambridge, MA 02141 (US). DAI, Mingshi [CN/US]; 7 Avondale Avenue, Billerica, MA 01821 (US). VOS, Tricia, J. [US/US]; One Willow Street, Apt. #2, Belmont, MA 02478 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

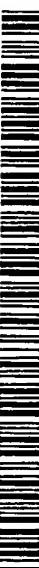
(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

(88) Date of publication of the international search report:
16 August 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 01/10842 A3

(54) Title: MELANOCORTIN-4 RECEPTOR BINDING COMPOUNDS AND METHODS OF USE THEREOF

(57) Abstract: MC4-R binding compounds of the formula (I): B-Z-E wherein B is an anchor moiety, Z is a central moiety, and E is an MC4-R interacting moiety are discussed. Methods of using the compounds to treat MC4-R associated disorders, such as disorders associated with weight loss, are also discussed.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/21327

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C07D235/06	C07D239/06	C07D233/20	A61K31/4184	A61K31/4164
	A61K31/505	A61P3/04			

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 731 408 A (HADLEY MAC E ET AL) 24 March 1998 (1998-03-24) <p style="margin-left: 40px;">examples IV,VI; tables I,II,III</p> <p style="text-align: center;">----</p> <p style="text-align: center;">-/-</p>	1,2,10, 11, 94-113, 124,125, 127, 132-136, 201

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

8 February 2001

Date of mailing of the international search report

22/02/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
 Fax (+31-70) 340-3016

Authorized officer

Hass, C

INTERNATIONAL SEARCH REPORT

Int'l. Application No
PCT/US 00/21327

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 47316 A (MILLENNIUM PHARM INC) 18 December 1997 (1997-12-18) page 49, line 29 -page 50, line 13; claims 13-17, 23-26 --- M. A. BEDNAREK ET AL.: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 261, no. 1, 1999, pages 209-13, XP002159223 abstract; tables 1,2 --- C. HASKELL-LUEVANO ET AL.: JOURNAL OF MEDICINAL CHEMISTRY, vol. 40, no. 11, 1997, pages 1738-48, XP002159224 figures 1,2; table 1 --- A. KASK ET AL.: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 245, no. 1, 1998, pages 90-3, XP002159225 abstract; figure 1 --- GB 1 418 053 A (BASF AG) 17 December 1975 (1975-12-17) page 3, line 27 - line 51 page 4 examples 4-8, 12-18, 22, 24-28 claims 1,12 --- WO 99 64002 A (PATCHETT ARTHUR A; PLOEG LEONARDUS H T V D (US); YE ZHIXIONG (US);) 16 December 1999 (1999-12-16) page 6 -page 10, line 3; claims 1,14 ---	1,2, 11-13, 94-113, 124,125, 127,129, 130, 132-136, 200,201 1,2, 94-113, 124,125, 132-136, 201 1,2, 94-113, 124,125, 132-136, 201 1,2, 94-113, 124,125, 132-136, 201 114,116, 117,119, 121-123, 205, 208-213, 215,217, 219-221 1,2,11, 94-113, 124,125, 132-136, 201
P,X		

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No

PCT/US 00/21327

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5731408	A	24-03-1998	US	6054556 A	25-04-2000
WO 9747316	A	18-12-1997	US	5908609 A	01-06-1999
			US	5932779 A	03-08-1999
			AU	723135 B	17-08-2000
			AU	3383697 A	07-01-1998
			BR	9709684 A	09-05-2000
			CA	2257857 A	18-12-1997
			CN	1227496 A	01-09-1999
			EP	0915706 A	19-05-1999
GB 1418053	A	17-12-1975	DE	2219841 A	25-10-1973
			CH	579054 A	31-08-1976
			FR	2182994 A	14-12-1973
			JP	49020171 A	22-02-1974
			US	RE32154 E	20-05-1986
WO 9964002	A	16-12-1999	AU	4680199 A	30-12-1999